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Review

Development of functional imaging in the human brain (fMRI); the University of Minnesota experience

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ABSTRACT

The human functional magnetic resonance imaging (fMRI) experiments performed in the Center for Magnetic Resonance Research (CMRR), University of Minnesota, were planned between two colleagues who had worked together previously in Bell Laboratories in the late nineteen seventies, namely myself and Seiji Ogawa. These experiments were motivated by the Blood Oxygenation Level Dependent (BOLD) contrast developed by Seiji. We discussed and planned human studies to explore imaging human brain activity using the BOLD mechanism on the 4 Tesla human system that I was expecting to receive for CMRR. We started these experiments as soon as this 4 Tesla instrument became marginally operational. These were the very first studies performed on the 4 Tesla scanner in CMRR; had the scanner become functional earlier, they would have been started earlier as well. We were aware of the competing effort at the Massachusetts General Hospital (MGH) and we knew that they had been informed of our initiative in Minneapolis to develop fMRI. We had positive results certainly by August 1991 annual meeting of the Society of Magnetic Resonance in Medicine (SMRM). I believe, however, that neither the MGH colleagues nor us, at the time, had enough data and/or conviction to publish these extraordinary observations; it took more or less another six months or so before the papers from these two groups were submitted for publication within five days of each other to the Proceedings of the National Academy of Sciences, USA, after rejection by Nature in our case. Thus, fMRI was achieved independently and at about the same time at MGH, in an effort credited largely to Ken Kwong, and in CMRR, University of Minnesota in an effort led by myself and Seiji Ogawa.

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Introduction

This article is closely related to another titled “The Road to Functional Imaging and Ultrahigh Fields” that I wrote for this volume (Uğurbil, 2012-this issue). The other article focuses on the development and the use of high and ultrahigh magnetic fields in functional magnetic resonance imaging of brain activity (fMRI), and takes a longer “historical” perspective on events that shaped my career in magnetic resonance. Inevitably, however, such a topic includes the history of the development of fMRI since high fields and fMRI are intricately tied in my career. The very first human imaging experiment that I ever undertook was the experiments aimed at developing fMRI using the very first human imaging instrument my lab acquired at the University of Minnesota; this instrument was a “high field” human system operating at 4 Tesla, at a time when 1.5 Tesla was the prevalent clinical MR scanner and 3 Tesla clinical scanners of today did not exist. Until very recently, in fact, I would have been

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able to say I never worked on functional imaging, or any other imaging for that matter, at a field strength lower than 4 Tesla. That record was altered in the last year with work on 3 Tesla, launched due to the Human Connectome Project (Van Essen and Ugurbil, in press).

Functional imaging

In the two decades since its discovery, blood oxygen level dependent (BOLD) fMRI has undergone a revolution, going from early experiments demonstrating relatively coarse images of activity in the visual cortex to mapping cortical columns and to "brain reading" that constructs mental experiences of an individual, all using the fact that we were endowed with a complex paramagnetic molecule sequestered in our blood vessels and that neuronal activity has spatially-specific metabolic and physiologic consequences. We at the Center for Magnetic Resonance Research (CMRR), University of Minnesota, were fortunate to be one of the groups that independently initiated and conducted the experiments that introduced fMRI (Ogawa et al., 1992).

Bell labs connection

The attempt to develop fMRI in CMRR came about because of the work Seiji Ogawa did in Bell Labs introducing the BOLD effect (Ogawa and Lee, 1990; Ogawa et al., 1990a, 1990b) (also see Ogawa, in press). These early experiments conducted on rats did not show functional mapping; rather, they demonstrated that metabolic perturbations such as hypoglycemia and graded levels of oxygen in the inhaled gas mixture affected the visibility of venous blood vessels. I was very much aware of this work not only because of my scientific interests at the time but also because Seiji and I knew each other well; we were colleagues that had worked together for several years in the same group in Bell Laboratories, driven with the aim of establishing *in vivo* applications of the magnetic resonance phenomenon.

After receiving my Ph.D. in Chemical Physics at Columbia University in 1977, and after serving four months in the Turkish army (the Marines to be specific) to fulfill my obligatory military duty, I joined the Biophysics Department in Bell Laboratories. The Department was led by Robert Shulman; I was his postdoctoral fellow, working on the development of MR spectroscopy for the study of intracellular processes in intact cells. Seiji Ogawa and Truman Brown were members of this department and were involved in the intact cell work. Later, Jan den Hollander, Sheila Cohen and Bob Gillies would join us. Gil Navon was there before my time but would visit us on occasion and participate in the effort when I was there as well. We employed ^{31}P and ^{13}C NMR spectroscopy to study energetics and metabolism in *E. coli* and yeast cells in suspension (e.g., (Ugurbil et al., 1978a, 1978b, 1982; Shulman et al., 1979)). The work from this lab together with the contemporaneous effort from the laboratory of George Radda at Oxford University pioneered *in vivo* magnetic resonance spectroscopy or MRS that many employ today to study metabolism in the human body using high and ultrahigh magnetic fields.

Although we specifically worked on spectroscopy studies directed at *in vivo* metabolism, the general scientific theme that excited us was the use of magnetic resonance to obtain information non-invasively about biological processes in intact systems. At the time, knowledge on the structure of biological molecules such as proteins, RNA and DNA were being expanded at a dizzying rate, supplementing already extensive but rapidly increasing understanding of enzyme kinetics and regulation of metabolic pathways. Such knowledge, however, was derived from preparations obtained from cell extracts; we wondered, if data garnered by these destructive techniques were applicable in the complex *intracellular* environment of the intact cell. Oxidative ATP synthesis, a problem I worked on in Bell Labs and continue to work on even today in Minnesota sporadically, is a good example. It requires the intact bacteria (or in eukaryotes, at least the intact mitochondria) to function. It was a hotly debated topic at the time; the Mitchell hypothesis that assigned a critical role to an electrochemical H^+ gradient across the bacterial (or equivalently mitochondrial) membrane was pitted against concepts of an intermediary chemical compound that mediated the coupling between the electron transport chain and the ATP synthase. The proof of the latter required isolating this compound and showing that, in an isolated preparation, it could drive the conversion of ADP and inorganic phosphate (P_i) to form ATP. The former hypothesis, on the other hand, required working with intact bacteria or mitochondria. Although Mitchell and others provided evidence for the "Mitchell hypothesis" by looking at proton extrusion in mitochondrial suspensions, leading to the Chemistry Nobel prize for Peter Mitchell in 1978, arguably we were the first to detect this as a transmembrane H^+ gradient directly by visualizing the difference between intra- and extra-cellular pH in suspensions of E. coli (Ogawa et al., 1978a, 1978b; Ugurbil et al., 1978a, 1978b, 1979, 1982) and mitochondria (Ogawa et al., 1978a, 1978b). One can see from these references that Seiji and I worked on similar problems in the same group at about the same time. Even though most of the time we were not co-authors in the same papers, the entire group was tightly knit through the excitement, and enthusiasm we felt for the work we were engaged in.

Clearly, we ultimately thought about human experiments; chemical shift imaging (Brown et al., 1982) which came from this Bell Labs period is testimony to this ultimate aspiration. However, as good physicists and physical chemists, we had taken the reductionist approach to start with the simplest system possible, the canonical bacteria *E. coli*, but with the dream that one day we would ultimately achieve, with similar magnetic resonance methods, human studies of physiological processes *in vivo*. Functional imaging came about as a chapter in this general saga. Seiji eventually moved from working with *E. coli* to working on the brain of rodents with imaging; he recently told me that he was interested in the neonatal brain and switched to imaging because he was skeptical that spectroscopy would work in such small brains. His interest in the brain fitted well to the transformation of the Biophysics Department in Bell Labs that occurred when Bob Shulman, and many others including myself, left Bell Labs. Under advise from John Hopfield, a member of our department at the time, the Biophysics Department was redirected towards neurosciences, hiring individuals like David Tank and others. Thus, Seiji found himself immersed in a neuroscience environment where his interest in the brain found a natural home.

I also abandoned cell suspensions starting at about the same time to work with perfused heart models. This model possessed inherent solutions to many difficulties encountered with cells in suspension; it had a high cell density (better for signal-to-noise ratio (SNR)) than what is achievable with cells in suspension, it had its own vasculature that enabled the delivery of ample oxygen simply through perfusion, and it could perform work and hence attain commensurate oxygen consumption over a large range by simple external manipulations, such as pacing or pharmaceutical interventions. I was not necessarily interested in the heart *per se* as a cardiologist would be; I was being opportunistic, scientifically speaking, in adopting it for studies of oxidative energetics. Of course, it also helped that upon my arrival in Minnesota, among the many people I talked to, cardiologists showed the greatest interest in collaborating with me, leading to close working relationships with Arthur From, Mark Petein, John Foker, and Robert Bache, and others in the University of Minnesota, all clinicians and cardiac researchers. The perfused heart experiments were followed with open-chest instrumented heart studies in large animal models, closed chest instrumented animal models and ultimately humans at 4 Tesla, demonstrating the claim I have made that we did aim to go to humans from the very beginning.

When I moved to Minneapolis in 1982, I initially started working with a vertical bore 8.4 Tesla system. Subsequently, I acquired a 4.7