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Echo Planar Imaging before and after fMRI: A personal history

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Abstract

Echo-planar imaging (EPI) plays a crucial role in functional MRI. Focusing especially on the period from 1988 to 1992, the authors offer personal recollections, on the development of practical means of deploying EPI, the people that participated, and its impact on MRI in general.

Keywords

History; fast imaging; technology; BOLD; fMRI; Advanced NMR Systems; Instascan; gadolinium

Mark Cohen (MSC): For me, it started in 1987 at the Topical Conference on Fast MRI Techniques in Cleveland. Low flip angle imaging was the rage, as workers in the field tried to reduce clinical scan times to tolerability. At that conference, Richard Rzedzian, who had trained under Sir Peter Mansfield, showed a video of transaxial cardiac images that he, and his colleagues Ian Pykett and others at Advanced NMR systems (ANMR) had acquired on a homemade, purpose-built, 2.0 Tesla echo planar imaging (EPI) device that they called, "INSTASCAN". From my perspective, I had just seen the future of MRI. I decided on the spot to find out what I could do in this new field. No one at my current employer, Siemens Medical Systems, would admit to any practical interest in EPI (but as we all later discovered, Siemens was waging a parallel effort, discussed below). Within a matter of a few weeks I therefore made up my mind to find a job at ANMR. In the short period between my ANMR interview, and my move to Massachusetts in 1988 to take charge of their applications effort, the company had signed a contract to accept an existing General Electric Signa® 1.5T scanner and to add echo-planar imaging capability to it.

EPI had been discussed some years earlier by Mansfield, in a prescient paper entitled, *"Multi-planar image formation using NMR spin echoes."* (Mansfield, 1977). There were distinct problems with the zig-zag k-space trajectory that he described, but all of our technical work at ANMR could be seen as extensions of this remarkable idea. Richard Rzedzian directed the MRI research efforts at ANMR while Ian Pykett managed most of the financials and operations. Rzedian was a dynamo. He was on a personal mission to bring an instrument to market that would outperform any competition – even when that competition included major and well-financed companies such as General Electric, Siemens and Philips. I was tantalized by his entrepreneurial spirit, and by the chance to be in on the ground floor

of a new company. Richard was extremely demanding of the engineering team at ANMR who made up the majority of its employees. He was hot-tempered about schedule delays and by anyone's attempt to compromise performance or specifications. He could do this because he was versed and capable at almost any level of detail from transistor to industrial design. The specifications on that system were themselves incredibly demanding. For example, to achieve the energies needed drive the high amplitude fast EPI gradients while keeping real power modest, the ANMR system utilized a resonant coil set, with the inductive coils in series configuration with large capacitors. By adding just enough energy to compensate for the resistive losses, the ANMR gradient set generated sinusoidal waveforms without the need for ultra-high power linear amplifiers. The sinusoidal shape meant, though, that signal digitization at a constant rate would result in raw data that were not on a Cartesian grid. We therefore performed our sampling on a cosine timing schedule. For this to work, it was necessary that we could ensure that an equal area of k-space (constant gradient-time product) was covered between each sample. This tough requirement was, in turn, played out in an exotic power controller that added energy just as needed to ensure the gradient-time product.

The budget for the GE retrofit was a mere $1 million, plus the loan and service of the Signa sited at ANMR. Although ANMR enjoyed private investment support we were always worrying over costs. Rzedzian was relentless in demanding ever more performance within the same fiscal constraints. To make matters worse, midway through the project, to our utter shock, General Electric demanded a renegotiation of its contract to deliver the same outcome (EPI on a Signa in one year) for less money. After all, we were in no position to back out. Subsequently, we learned that GE, too, was mounting an internal effort, but I can only speculate as to whether this was a factor in the contract questions.

The scientific staff was tiny; when I arrived, physicist Michael Rohan had been at the company as one of their very first employees, and was underway designing high performance self-shielded gradient coils. Robert Weisskoff had been newly recruited out of MIT, but had no particular MRI experience, so I had the singular privilege of teaching him everything I knew about MRI (I spent the next ten years learning about MRI from him, but that is part of a different story). The Signa arrived a month or two after I got there. After it was up and running to GE specs, Richard, Robert and I got out our hand tools and started taking apart Signa to figure out how it worked and to begin the retrofit development. When I disassemble electronics, I remove the nuts and bolts, separate the parts, then replace the nuts onto their original bolts. This helps me to remember what went where. Robert, on the other hand, would place the nuts in his pockets, whereas Richard would place them in a small pile on the floor near where they came out. Despite this obvious anarchy, we worked with confidence that we would someday be able to put the Signa back together (Figure 1).

Weisskoff and I could not have had much more fun. For all intents and purposes, the scanner was ours to play with as we pleased. The technical staff at ANMR was extremely talented, and we were able to make outrageous requests, such as insisting of Tim Bowe, who led the software engineering group, that we have a rapid development environment in which we could script real-time image processing. This was well before the heyday of silicon valley and the creation of modern software development environments. It may seem like a relatively small advance now, but while the ANMR system had its own real-time scripting language, the Signa platform was written using a macro assembler called, "ppl", with compile times of hours for single sequences. Late at night, as we waited for the GE ppl sequences to compile Richard, Robert and I competed in death-defying two wheel wheelchair races through the research labs, not to mention the paper airplane, spitball and other classy competitions. Weisskoff and I, in particular, were in the lab almost continuously – late nights and many weekends.

The power of EPI was, and is, remarkable, but its major applications were entirely unknown at that time. As part of understanding these, we invited forestry scientists to scan logs (Chang et al., 1991) and hydrophysicists to look at fluidized bed s (Kytömaa and Cohen, 1991); the latter work was motivated by Van Wedeen, a true creative genius from the MGH-NMR center. We made whole brain angiograms fast enough to see pulsatile changes in blood flow. We scanned joints in motion (Cohen et al., 1990a), cancer-infested livers – almost anything we could imagine. In one project we modified the patient table to allow it to move continuously during scans so that we could perform 3 mm isotropic scans of the entire body in a minute or two: “infinite”-tr T2-weighted scans as the body moved in, followed by T1-weighted inversion recovery scans as the body moved out. In my opinion, many of these applications remain important to this day, but have yet to be exploited. It was my good fortune that Felix Wehrli, then at General Electric, came by for a visit. I presented many of these applications at a plenary lecture at the SMRI in 1990 on his recommendation. A review by myself and Weisskoff in 1991 sum marizes about a year and a half of truly exciting work at ANMR, probably the most productive time of my research career, and covers much of the technology of EPI in detail (Cohen and Weisskoff, 1991).

One of Rzedzian’s insights was that EPI could be extended readily to allow “multi-shot” acquisition. He laid out and patented two means, “Mosaic” and “MESH” that each allowed better k-space coverage, and therefore improved resolution. We harnessed the partial k-space ideas that Paul Margosian had developed for fast imaging (Margosian, 1985), allowing us to acquire EPI data with very short te. All of these have since become standard tools in commercial MRI.

FLASH vs. EPI

As it happens, not everyone was equally excited by EPI. Before EPI there was FLASH, a low flip angle fast imaging technology patented by Jens Frahm, Axel Haase, and others (Frahm et al., 1998) that was used under license by the major instrument vendors. The FLASH technology was, and is, extremely important as a means of managing imaging time, radio frequency heating and other factors. It is also not nearly as dependent on high performance gradients as is EPI. The FLASH patent was also extremely lucrative for its inventors, adding a certain heat to the discussions. At some point during all of this, I found myself in public debate with Jens Frahm about the relative merits of FLASH vs. EPI. As it happens, there are few areas where the methods currently act in opposition. While FLASH-based technologies have clear advantages in high resolution applications, such as Time of Flight Angiography, to date EPI is the method of choice for really high speed imaging, as used in functional MRI.

What is EPI for?

Some of the tricks we developed or learned during the period that Weisskoff and I worked at ANMR might still have potential. For example, Weisskoff showed that one could perform image-based field shimming in real-time by examining metric distortion of the images. While image-based shims are now common, the real-time shim might well be useful to perform regional shims. I became interested in a configuration where the patient table moved continuously as the scanner collected one slice at a time: perhaps T2 weighted images as the patient went in, and inversion recovery scans as the patient came out – an idea that was motivated by our scanning of hardwood. This whole-body scan topic is still dear to my heart and could be developed as a low cost well-patient exam with a single slice scanner.

The team at ANMR had a clear understanding that their focus and future was to be cardiac imaging. I arrived with experience in triggered and gated cardiac work and had little reason to believe that taking faster pictures was the answer to the many clinical challenges in

cardiac MRI. Besides, I had my Ph.D. in neuroscience and didn't find the organ terribly interesting. Instead, based on a hunch and stubbornness, I set about to turn ANMR into a brain imaging shop. My arguments were these: At the time, approximately 65% of all MRI scanning procedures were in neuroradiology, with the balance being musculoskeletal, hepatic and other visceral studies. The heart was an also-ran, that occupied much less than 5% of the MRI clinical effort and was not likely to be the big payoff. In fact, cardiac MRI is no more prevalent today. Important brain imaging was on the other hand, it was challenged by massive problems of scan times, usable contrast, motion and others. Further, brain images were the image quality standard. Therefore, I argued, we had to produce high quality brain images to be credible to our customers. My own goal was to create clinically competitive cranial images in seconds. To this end, we worked by progressively upping the spatial resolution of the scans using multi-shot methods, and steadily improving contrast. About a year later, at MGH, we did a demonstration that we could run as many as six diagnostic quality brain studies (proton density, T2, Inversion Recovery at 1.5×1.5×5 mm resolution) in one hour using the ANMR system.

We were fortunate that Robert McKinstry, a graduate student of Bruce Rosen, became interested in diffusion imaging. McKinstry was given a seat in the office that Weisskoff, Rohan and I shared; motivated in part by the work of Denis LeBihan and Bob Turner he set out to collect some of the earliest diffusion-weighted brain scans (McKinstry et al., 1990a; McKinstry et al., 1990b) that became the infrastructure of the now large scale effort in diffusion weighted protocols for stroke imaging and for fiber tractography. Weisskoff's work on thermometry was an offshoot of McKinstry's efforts. We had hoped that it might be valuable in image-guided laser surgery (Bleier et al., 1991).

At the same time, Bruce Rosen and Arno Villringer at the MGH-NMR center were exploring ideas of susceptibility contrast imaging. They had shown that after pulsed injections of Gd-DTPA, or dysprosium compound s, the MRI signal could be dropped to a small fraction, as the bolus of contrast agent traversed the vascular system. In principle, this could be used to quantify blood flow. My good fortune in being the ANMR applications scientist allowed me to manage a collaboration with this group. John (Jack) Belliveau, was Rosen's trainee and believed with a deep passion that these methods could be used to track blood flow in the brain and that, importantly, they would be sensitive enough to detect vascular changes associated with brain activity that had been reported previously with Positron Emission Tomography. After some negotiation with the MGH investigational review board, Jack and his MGH colleagues made the trek to ANMR to test his theories. They brought over a volunteer, a pair of blinking LED goggles loaned by Peter Fox, some gadolinium contrast agent (Magnevist®) and some syringes, and we got going.

The ANMR scanner was the *still-in-prototype* modified GE Signa. The EPI components were integrated very loosely: we replaced the Signa gradient system with a lower inductance, higher capacity system that Mike Rohan had designed (more on this below), and we modified a few GE pulse sequences to output some simple control pulses. The X or Y gradient coils could be quickly assigned to either the original Techron power systems or to ANMR's resonant controller. To capture the RF signal we simply inserted a buffered "T-connection" into the analog train. ANMR's standalone pc's performed all of the image processing. There were crucial failure modes.

Belliveau's contrast agent method of functional brain mapping requires two injections of Gadolinium-DTPA, which has a blood half-life of tens of minutes. The total dose is limited, so we split the injections into two equal doses at half the allowable maximum. In practice, this meant that we had one try per subject at this experiment. A first injection was performed with the subject in darkness, and a second was performed 45 minutes or so later in the

presence of a flashing light stimulus. Interestingly, closely echoes the original visual activation studies by Mazziotta and Phelps (Mazziotta et al., 1981; Phelps et al., 1981).

In one joint experiment with the MGH group, after a first injection we captured a series of about one hundred serial EPI scans and saved them off to disk, then waited to try again, after a suitable clearance interval, in order to make a comparison scan. The second injection didn't go quite smoothly however. The data were collected into our pc (the ANMR host computer was supported by the then mighty Intel 80386), which immediately locked up before they could be saved. We knew that we were not going to acquire another thing with that computer without rebooting it (and thereby losing all of the precious functional imaging data then stored in main memory.) Enter Steven Morelock, a parrot - toting pirate of a computer hacker in the software group at ANMR. With incredible poise and confidence, Steve announced, "I can take care of that, just give me a few minutes." Within an hour or so, Steve returned with a floppy disk and some code. He had just created a memory browser tool that we could use to display the images currently in volatile RAM and, with a cross-hair cursor, visually select the beginning and end of our contrast agent series and flush these data to disk. This remarkable feat saved the experiment, not to mention a great deal of face for the team at ANMR.

Between the time that we collected those data for Belliveau's experiment, and the time that we wrote up the study for submission to *Science*, Rosen and Center Director, Tom Brady, had successfully wooed me to jump back from industry to academia, where I took on the direction of the "*Hyperscan*" imaging lab – the first installation site of ANMR's retrofit product. A large group contributed heavily to making that publication possible. I'd like to single out especially Michael Vevea – the NMR Center's brilliant computer specialist, who did some extraordinary coding to allow the signal integration that enabled the contrast mapping, and David Kennedy who made the tools that allowed us to register our single slice activation study with high resolution T1-weighted head images of the same subject. With their help, the task was given to me to create what became the cover image of the *Science* magazine containing Belliveau's report (Figure 2).

Interestingly, at the time we had little precedent as to how to present functional images of the brain. In creating what I expected at the time was destined to become a pivotal image, I then chose the particular color scale of red to yellow to indicate increased blood volume and dark blue to cyan to indicate decreases – similar to the conventions used in Positron Emission Tomography to indicate absolute signal. I bother to note this because I've grown to regret this and a few other decisions about the picture. Notably, the semiotics of color are such that red-yellow colors instantly nominate themselves to our attention as important and meaningful, whereas the cooler colors don't draw us in. Thus, in my darker moments, I feel that this decision has colored the field of fMRI in attending principally to blood flow increases rather than equally to increases and decreases; a strange effect that biases our interpretations. Sadly, this is another digression in a longer history.

As Director of the MGH-NMR Center's *Hyperscan* lab, I was empowered to set a schedule to use the equipment. The more senior members of the lab were given about half a day each week during daytime hours to do their work, with others given access in the nights and evenings. As a whole, there was a great deal of interest in the Center for susceptibility contrast imaging – arising from a program grant on this topic to Rosen and Brady. Very notable was the work of Keith Thulborn who was interested in exploiting the susceptibility differences of oxy and deoxy-hemoglobin to study various aspects of metabolism. This was a very dynamic lab, and we were in contact with terrific colleagues, one of whom was Robert Turner, then at the NIH, who had been exploring the signal losses associated with oxygen suppression in cats using his own home-built small EPI coils.

It was thus in the air that someone would put together the pieces that ultimately became BOLD functional MRI (fMRI). As will appear elsewhere in this special issue, it was Kenneth Kwong who performed the first crucial human experiment1 in May of 1991. Rather then repeat what he can better tell, I'll just add a little color commentary.

Ken Kwong was not employed at the NMR Center. Instead, he was visiting the Eaton-Peabody Laboratories of the Massachusetts Eye and Ear Infirmary, a leading center for the study of auditory neurophysiology. Ken had one of our nighttime slots. He was in the lab at all hours, such that we openly doubted whether he had a place to sleep – perhaps under the scanner console. The NMR center was set up in such a way that the more established faculty had offices upstairs, while the scanner was downstairs, as were the student workspaces. When Ken brought upstairs what were later recognized as proof that the BOLD effect could be used to look at brain activation I, and in my recollection everyone else, responded with a comment akin to, "nice artifact, Ken." It frankly felt far to good to be true that anyone could simply lie in a scanner having their picture taken and thereby reveal their brain's functional activity. Fortunately, our skepticism did nothing to damage Ken's enthusiasm. After a few rounds of replication, all were convinced.

Recognizing immediately how important this discovery was, we collectively did our best to give it the high profile we felt it deserved. Flush with the excitement of appearing in *Science* with Belliveau's paper, we tried again with Kwong's results. This time, the editors were much less enthusiastic, citing Belliveau's work as evidence that this was no longer novel. It's tempting to glibly state that the editors there lacked vision. Practically speaking though, MRI research was the domain of clinical specialty journals, and few basic scientists were in much of a position to understand the dramatic difference between functional brain imaging with and without injected contrast.

At a truly personal level, I am trained principally as a neuroscientist, based on a long-standing passion for understanding human consciousness. I was, and am, intensely interested in how the physical processes of the brain give rise to the particular shape of human cognition. My doctoral work was in classical neuro-electrophysiology, where I explored brain and chemical modulatory effects on spinal reflexes. At the time, however, we were still recovering from the excesses of B.F. Skinner's *radical behaviorism* (Skinner, 1976), which had no place for internal states such as consciousness or thoughts. Thus, eager students like myself were discouraged from talking of such things. For my part, I realized that even if I were to place a recording electrode into every neuron in an animal's brain I would never have the remotest idea what it felt like to be that animal. There was no practical means for breaking out of this particular intellectual box, and certainly none that justified what I perceived to be the slaughter of lab animals at my own hands. Even before completing my doctorate, I had decided to abandon the field to pursue a dream of making an impact in low-cost medical technology.

The pioneering work that resulted in the discoveries of Belliveau, Kwong and Ogawa of course changed the face of cognitive neuroscience. As I saw it in 1991, we had opened a small chink in the armor that separated mind from brain and it has become mission since then to widen it so completely as to obliterate that barrier. For my part, it has been a twenty-year field day, allowing me to return to my first love in human neuroscience. Somewhere in the murky past I recall pushing for the acronym, "fMRI," to describe the new method.

[1]Surely there will be some controversy about priority. Ogawa's experiments were taking place in parallel and, to the best of my knowledge, in complete independence. Without in any way diminishing the genius of either group, the practical discovery of human BOLD imaging was clearly imminent.

Certainly, I remember debating this over beer with Bob Turner who was favoring the moniker, functional neuroimaging MRI, pronounced, “fun MRI.” He was probably right.

In the end, ANMR was an ambitious but impractical venture. The company was probably too naïve and certainly under-funded. Shortly after I left, they had a small number of commercial installations (one to our lab at UCLA) but never realized their dream of a standalone INSTASCAN camera. Siemens, and very shortly thereafter, General Electric, quickly took the lead away from our small group. Echo-planar imaging, on the other hand, has been an unqualified success. It is the enabling technology for most fMRI, for tractography, for MRI thermometry and many other applications. The gradient technologies embedded into the scanner to make EPI possible provide enormous benefits in other sequences as well, such as MP-RAGE and GRACE, that take good advantage of this performance.

Siemens was on the case, as well

While I can speak from experience at ANMR, unbeknownst to us, there was another group putting effort into a commercial product. I first became aware that a team at Siemens, led by Franz Schmitt, was working on EPI when we both submitted papers on peripheral nerve stimulation (PNS). Our prototype resonant gradient controller was capable of generating extremely fast switching rates. We had an original operating point of 1600 Hz along the readout axis, requiring a gradient amplitude of an amazing 4g/cm to achieve our targeted 3 mm resolution. Sadly, when we tested the scanner on ourselves, both Rzedzian and Weisskoff clearly felt mild sensations during as the gradients operated. We determined that this was a predictable result of current induction in the body from the time-varying magnetic fields. We unhappily published these results (Cohen et al., 1990b), which required a downscaling of the instrument performance to stay out of this range. The pictures taken with the faster gradients were noticeably better, for their reduced distortion and signal losses. As it happens, Schmitt and colleagues, with Tom Budinger, had come to a similar conclusion about PNS and presented similar findings just slightly later. At ANMR we would have been happier to see these results signed by that group, because we hated telling the world about potential safety problems with our instrument.

The challenge at Siemens was different than what we faced at AN MR, because they were working towards a complete integration with their already mature MRI product, while we were producing what we called “a wart on the Signa.” For example, a “ghost” artifact occurs when there is a line-by-line timing error in the EPI k-space trajectory. At ANMR, we carefully tuned the gradient amplitudes and timings to give us essentially ghost-free images at the highest EPI resolution without software correction, running the gradients at a fixed amplitude. The Siemens group, however, worked towards more flexibility in their field of view, requiring them to develop a phase correction scheme based on calibration scans (Schmitt et al., 1990). Even so, the Siemens device was already practical by 1991 (Schmitt et al., 1991) when that group replicated and extended the Belliveau findings on their own scanner.

Franz Schmitt (FS): The efforts at Siemens began in late 1987. Our work was motivated by Peter Mansfield’s initial paper on EPI and Mark Haacke’s early paper / abstracts on hybrid imaging (~1985 or so). I remember that in the late 1980’s, we had some visits from Peter Mansfield and some of his group. We tried to squeeze out as much information as possible, but they kept their lips tied. So we had to go through the full adventure of exploring a new (imaging) technology with all of its ups and downs. For sure, the formation of the ANMR company and their first EPI results caused us to speed up with our efforts significantly.

The group consisted of Hubertus Fischer, Helmut Barfus, Dietmar Hentschel, Ralf Ladebeck, Erich Reinfelder and myself. I was assigned from the MR product development group to steer the EPI work eventually over to a product. While the others worked in our Siemens "Medizintechnik" basic R&D group, headed by Arnulf Oppelt (the inventor of FISP and other MR methods). The group at our Siemens Corporate Technology research center, headed by Horst Siebold, designed and build the first EPI gradient (Z-only). The second whole body version was already vacuum potted, a method which is now the gold standard of manufacturing gradient coils (by Konrad Meyer, a great design engineer). We were forced to explore the vacuum potting; the ever present and annoying RF noise (also called "spikes") left no other choice.

My lab book on practical EPI work at the Corporate Technology facility started September 10, 1987. Theoretical work started earlier. Our first EPI head images were acquired at 2T with a head gradient insert. The EPI readout gradient amplitude was 27 mT/m. PNS was therefore not an issue as we know now well (head gradient sets are not really causing PNS).

According to my lab books, our first Echo Planar image of a small sphere phantom was acquired on October 9, 1987. We were wondering what the resulting image resembled: definitely not a sphere. Instead it looked like a pulled tooth due to its strong susceptibility artifacts. After learning how to shim properly the first axial *in vivo* brain Echo Planar image was taken on November 3, 1987.2

From March 1988 on, we were able to acquire reasonable sagittal image quality in the brain (figure 3). In May 1988 we had the first DEPI (Double Echo EPI) method working which acquired a GRE and SE in a single shot. This was presented at a European MR conference in Berlin. I think it was 1988. This method was used later in the fMRI scientific community for a while to separate BOLD effects from large and small vessels.

Our clear intention was to perform cardiac imaging with EPI. We acquired our first body images on April 25, 1989. Challenged by RF spikes we had to manually eliminate these contaminants from the raw data. At that time we also experience PNS. I was the first person in the scanner feeling the cramping sensation of PNS in the chest. Overall, the problem of PNS halted our EPI effort for quite a while (3–6 months) before we became clear-minded again and asked Tom Budinger to help explore the issue. The finding was then presented at the annual RSNA meeting in Chicago in 1989 by Hubertus Fischer and was later published in the Journal of Computer Assisted Tomography (Budinger et al., 1991). At that time we were scratching our heads why we were the only ones running into this issue. I.e., why did ANMR not report on this? In deed they had, at about the same time, similar experiences as I learned by talking to Mark Cohen during a long walk along the Point Reyes Peninsula north of San Francisco. I believe this was during the 1991 SMRM meeting.

Our first whole body EPI images have been acquired with a single series resonance L-C circuit in the Z direction (without any switch). The readout gradient pulse was calculated in such a way that during the rise up to full amplitude the echoes were placed right in the center of echo readout interval (at max of the sine gradient half wave). We called this the "RO prephasing". Later this level of technology, what we called "poor man's" EPI, was refined with Thyristor and IGBT semiconductor switches. Stefan Nowak was our main driver behind the power electronics efforts at that time and still is the leading figure in our gradient amplifier group. Early switch networks consisted of a serial and parallel Thyristor switches. In the final state it was an H-Bridge configuration (with slow IGBT transistors) which was commonly used in rectifiers, for example. Flexibility in pulse programming was

[2]MSC: Our first human image, of Richard Rzedzian, looked quite a bit like a large egg…

our main goal. The H-Bridge configuration with the capacitor C in the center of the H-bridge was the first step towards this target. However, only sinusoidal ramp EPI pulses could be used at that time. Later this configuration was extended to fast switching IGBTs with the gradient coil in the center of the H bridge (no capacitor was needed anymore). This is topology of our gradient amplifiers since 1996 (some special tricks apply).

From 1990 until 1992, Michael Stehling, an MD and PH D, joint our team. Michael did his PHD with Peter Mansfield on EPI and was very fruitful for our work in the early 1990ies. After sorting through the PNS issues, which forced us to go down with the magnet field strength to 1T, we could finally enter into *in vivo* and clinical work. Working at 1T was a pleasure, as susceptibility effects have been quite pleasing for body imaging. It allowed even nice body imaging. We had several liver patients coming in from Hannover. Peter Reimer, who had worked at MGH on the ANMR system (with Mark Cohen) before, was heading these efforts. With Stehling we entered the neuro research and clinical arena and made real advances. We scanned tumor and stroke patients (published in 1993) and started with gadolinium perfusion. At that time we knew already about Jack Belliveau's ground breaking work with human visual stimulation, in conjunction with bolus Gadolinium administration. We weren't yet aware however, of Seiji Ogawa's work on Bold. We replicated Jack's work and I remember very well when Michael Stehling bought a set of high magnification goggles. When wearing it, he looked very much like Jerry Lewis in his funniest movies.

Through a visit of Bob Turner, also a former fellow of Peter Mansfield, we got our introduction into the susceptibility contrast related functional MRI world. Bob told us in early 1991 about contrast agent based CBV, CBF and such, and also mentioned the respiratory challenge work he was performing in cats or monkeys, *i.e.* seeing a significant signal drop in T2* weighted imaging reduced oxygen. We tried a similar experiment then, with Michael Stehling as our volunteer in the EPI scanner who could hold his breath for 90 seconds. The signal drop we then experienced was on the order of 20%. This result was then reported at the SMRM in San Francisco in 1991. The abstract (See Figure 4) did not mention this experiment as it was performed between the abstract submission deadline and the SMRM meeting. However, the abstract showed what we had in mind with respect to visual fMRI (triggered by the results from MGH). A Siemens internal memo that I wrote about this SMRM paper notes a 20% signal drop of the breath hold stud y. This work was then published in 1993 (see…..)

In September 1992 we installed our first EPI scanner at the Beth Israel Hospital, (BIH) in Boston. It allowed 40 mT/ m gradient switching, with sinusoidal ramps, in 250μs. Remarkably, this gradient amplitude and switching time is still a "standard" performance specification of today's MRI scanners. Robert Edelman was the lead the EPI research team at BIH. Piotr Wielopolsky, the most gifted sequence programmer I ever met in my life, created most of the EPI sequences. He also used our EPI booster system to speed up conventional imaging, such 3D FLASH for TOF angiography. Bob's EPI work in the liver, segmented EPI in heart and especially his contribution to arterial spin labeling with EPISTAR (Edelman et al., 1994) were remarkable outcomes of that period.

Although we did not really have spare parts (only the bare elemental blocks, such as capacitors and IGBT transistors were available) we were very lucky to have that system running reliably for several years. However, the challenge of the RF spikes remained. At this time we used a whole body RF coil. I remember very vividly the frustrating situation with spikes. I had my colleague Ralph Oppelt (one of the most experienced RF engineer I ever worked with) come to Boston to figure out what the cause was. We did not really succeed during the first week of his stay and concluded to go to Cape Cod on the weekend. That weekend was VERY rainy. Humidity went up significantly, as before it was very dry. When

coming back from that nice weekend at Cape Cod, we sat down on the scanner on Monday morning and realized that all spike were gone. The miracle was the humidity. From that moment on we controlled the environmental air condition and put some humidifier into the scan room.3 Later on we fixed the RF coil also, and the researchers, Bob Edelman, Piotr Wielopolsky, Justin Pearlman and Steve Warach had all the freedom to play with that nice instrument.

Although it was great fun to see the fMRI work evolving at BIH, I honestly have to say, that I could not envision what effect EPI would have in the world of neuroscience. Understanding that EPI as a single shot imaging tool will not make it for cardiac imaging, I very well remember Steven Warach's first stroke patient work with diffusion. To me this was a milestone in turning EPI into something clinical.

Overall, I am very proud to have participated in that exciting times of early EPI. Working inside Siemens with the colleagues mentioned above and also exchanging with researchers from Nottingham, BIH and ANMR, Mark Cohen in particular, I consider as a very satisfying time of my professional life (Figure 5).

Some Closing Thoughts

We note that Matthew Bernstein, Robert Vavrek and others at General Electric were working on an EPI product concurrently with the ANMR project. We have little to say about this however, not because it was less important in any way, but because we have little personal knowledge.

Mark Cohen: In its earliest phases, the new science of functional neuroimaging was variously considered "brain mapping" or "neurocartography," terms that evoke localization of function as the scientific mission. As I see it, this point of view is only a few steps removed from Franz Gall's phrenology (Cohen, 1996). It's true that fMRI does give us an extraordinary view on regional specialization, but the brain does its work through the coordination of neural activity from neurons that are widely separated. Further, the oxygen signal in fMRI is clearly non-primary and may yet turn out to be epiphenomenological, having no causal impact on neuroelectric activity (though that view might be too pessimistic). What fMRI is best at, I feel, is nominating portions of the system that are transiently in play in complex tasks, and in doing so on human subjects, w here we can reasonably ask about the cognitive states associated with the fMRI signal changes. The principal work of the brain in cognition is almost certainly electrical, and secondarily chemical – it is certainly not oxygen consumption. Despite promising work by creative investigators like Sadleir and Woo – who have made great inroads in functional applications of electrical impedance tomography – it seems unlikely that any method based on MRI alone will be used to take the crucial next steps in understanding the dynamics of cognition.

If anything, it's remarkable that fMRI has held on to its primacy for two decades, rather than yielding to the next big thing. It has gotten old, and familiar, enough that we no longer perk up when we hear yet another thing that makes the brain "light up" (a description I detest – as it is utterly misleading). The societal impact of fMRI has been enormous on many levels. There is a banality now to new observations of the physiology of cognition. In surgical planning, fMRI has preserved many lives. Being one of the most expensive ways of doing neuroscience, it has deflected considerable scientific funding. As time moves forward, it will likely change personal privacy, as at least a limited mind-reading device.

[3] *MSC:* These spikes have been a thorn in the side for everyone. At ANMR, we concluded that they were the result of corona discharge, a non-sparking pathway for high voltages to pass current between adjacent windings of the gradient coils. Another source turned out to be the filter panels for the gradient power. Here, there was a corona path to ground. Kapton tape was the solution here.

Surely, functional MRI has changed my life. It has put me in the company of extraordinary and impassioned scientists, it has introduced me to my wife. It is my enormous pleasure to add a few words to this volume celebrating the first twenty years with the other authors who are both my colleagues and my dear friends. I insist to my students, however, that it is a passing phase – an impractically expensive and complex means of studying the brain at low resolution. Much of my own work now concentrates on the fusion of fMRI and electrophysiology – a process I've been working on since 1992. To make matters worse, fMRI is very dependent on field strength, but cryogenic magnets are unsustainable in a near future where are liquid helium resources are depleted. I hope that we can enjoy the ride for a while longer.

Highlights

- The history leading up to the first fMRI experiments is described
- The involvement of major scanner manufacturers is discussed
- Several EPI pioneers are described
- The general impact of EPI, beyond functional imaging, is considered and placed into a broader context

Acknowledgments

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Abbreviations

EPI	Echo-Planar Imaging
BOLD	Blood Oxygenation Level Dependent
ANMR	Advanced NMR Systems, Inc.

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Figure 1.
Richard Rzedzian (left), Robert Weisskoff (right) inserting the hand-wound, epoxy-covered, prototype echo planar gradient coil into the General Electric Signa scanner at Advanced NMR Systems in 1989.

Figure 2.
Cover art for the November 1, 1991 issue of *Science* magazine (Belliveau et al., 1991), the very first demonstration of MRI to show functional activity in the human brain. The author is shamelessly proud of this image.

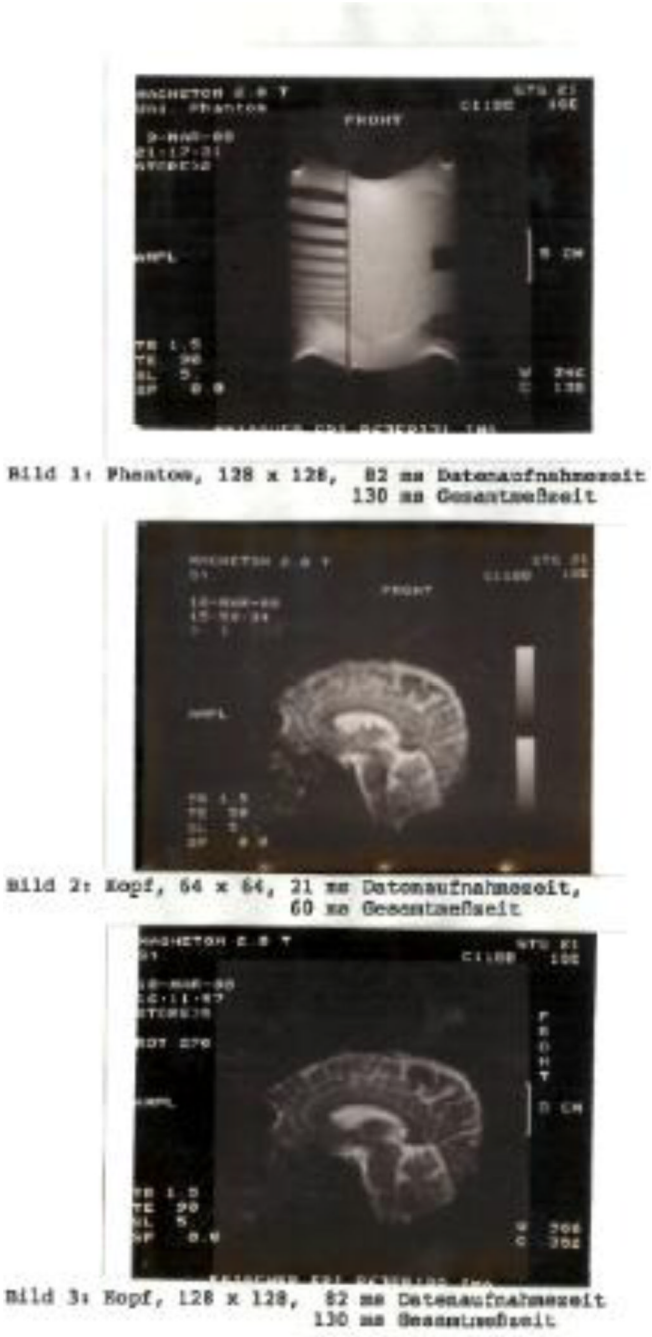

Figure 3.
A few of the early (1988) echo planar images acquired on the Siemens prototype scanner – from the notebook of Franz Schmitt.

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1991

Echo-Planar Imaging of Human Brain Perfusion at 1 T

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Purpose: To demonstrate that brain perfusion can be measured non-invasively with EPI (1,2) real-time MRI and to investigate the potential of this technique for the depiction of ischemic insults of the brain.

Techniques: Imaging was performed on our laboratory prototype, 1T echo-planar imager, with a resonant (595 Hz), non-shielded, whole-body gradient coil. The maximum gradient strength was 24 mT/m. No peripheral nerve/muscle stimulation were reported by the subjects. With a 128 x 128 pixel matrix and a FOV of 23 cm the 107 ms acquisition time images yielded an in-plane resolution of 1.8 x 1.8 mm, at 1 cm slice thickness. The data are acquired under an FID with echo time of TE = 60 ms. 100 sequential T2*-weighted EPI images of the brain of volunteers were recorded every 1.25 seconds during and after bolus injection of 0.2 mmol/kg BW Gd-DTPA. The injection through a catheter placed in the antecubital vein and extending into the superior vena cava started after the 5th EPI-shot and took 4 - 5 seconds to complete.

Results: The signal attenuation in gray matter and basal ganglia was observed (Fig. 1) 13 seconds after the injection , simultaneously with a feeling of heat in the face reported by the subjects. Signal attenuation in venous structures was observed 1.5 seconds later. In grey matter the maximum observed signal attenuation ranged from 45 - 75 %. Signal loss was due to susceptibility induced spin dephasing caused by the concentrated Gd-DTPA in cerebral vessels.

Discussion: Even at 1 T EPI is sensitive enough to depict brain perfusion exploiting the susceptibility contrast obtainable with concentrated Gd-DTPA boli. Regional perfusion differences in normal volunteers and patients can be observed and can provide useful information about malperfusion in cerebral ischemia. We are currently investigating the depiction of cerebral malperfusion in patients with stroke and the feasibility of functional imaging of the brain before and during optical stimulation; the results of these studies will be presented at the meeting.

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2) M.K.Stehling et al.SMRM 89, Book of Abstract, p. 358.

Figure 4.
SMRM abstract by Schmitt, *et al.*, for the 1991 society meetings in San Francisco.

Figure 5.
The authors at a private topical conference in Olema (1991?), where the former competitors shared notes on EPI.