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Record of a Single fMRI Experiment in May of 1991

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Abstract

The discovery of BOLD fMRI at MGH in May 1991 was 1) built on the on-going effort to develop new MR techniques for perfusion measurement with intrinsic blood contrast, 2) supported by the critical MGH expertise and experience on magnetic susceptibility and deoxyhemoglobin research, 3) inspired by the breakthrough in brain fMRI using dynamic susceptibility contrast (DSC) of the external contrast agent Gd-DTPA, 4) facilitated by the flow-BOLD insight of a hypoxia experiment, and 5) made possible by the availability of clinical echo planar imaging (EPI). The simultaneous demonstration of flow-weighted fMRI derived its intellectual origin from work on steady state arterial spin labeling (ASL). The free-wheeling and fertile intellectual environment structured by Dr. Thomas Brady and Dr. Bruce Rosen at the MGH-NMR Center provided the indispensable support for highly risky ideas to roam and succeed. The paper offers a first person account of the steps that led to the May experiment and its aftermath.

Keywords

fMRI; deoxyhemoglobin; BOLD; perfusion; ASL; magnetic resonance imaging; brain

On May 11, 2011 at the plenary session of the International Society of Magnetic Resonance in Medicine (ISMRM) annual meeting at Montreal, Dr. Bruce Rosen of the Massachusetts General Hospital (MGH) gave a brief introduction to the beginning history of fMRI, almost exactly 20 years to the date of the May 9, 1991 (Kwong, 1998; Kwong and Chesler, 1995) demonstration of MRI mapping of visual cortex activation by intrinsic blood contrast. After giving a review of Dr. John Belliveau's first fMRI breakthrough (Belliveau et al., 1991) of brain imaging using the dynamic susceptibility contrast (DSC) of Gd-DTPA, Dr. Rosen played a rerun of a movie of brain activation based on the deoxyhemoglobin contrast, the same movie presented in August, 1991 by Dr. Thomas Brady at the plenary session of the Tenth annual meeting of SMRM, the predecessor of ISMRM. Nestled in Dr. Rosen's presentation was also a page from my log book dated May 9, 1991 (Fig. 1) recording the design and MR parameters of the successful fMRI experiment that explored the power of the intrinsic blood contrast.

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The role of deoxyhemoglobin on the effect of the MR parameter T2 was known to me through the work of Dr. Keith Thulborn (Thulborn et al., 1982) who was a radiology resident at MGH in early 1991. I was not yet aware of Dr. Seiji Ogawa's published results in 1990 (Ogawa and Lee, 1990; Ogawa et al., 1990a; Ogawa et al., 1990b) on blood-oxygen-level-dependence (BOLD) contrast, now a synonym for the MRI contrast of deoxyhemoglobin. Dr. Thulborn's comments on deoxyhemoglobin and magnetic susceptibility alerted me to the possibility of selecting the gradient echo sequence, known to be highly sensitive to the susceptibility contrast, as a vehicle to look for blood signal change in the brain given sensory and cognitive stimuli. In the 3–4 years leading up to 1991, MGH was literally a hot bed for MRI research in susceptibility contrast. Great strides have been made in the use of spin echo, asymmetric spin echo and gradient echo MR sequences (Belliveau et al., 1991; Fisel et al., 1991; Rosen et al., 1990; Villringer et al., 1988; Wismer et al., 1988) to deepen understanding on the various manifestations of magnetic susceptibility in terms of T2 and T2* weighted contrasts. The intense research activities going on around me provided the indispensable intellectual guidepost and inspiration for my investigation of deoxyhemoglobin signal contrast for functional studies. After the presentation of our fMRI results at the August 1991 meeting of SMRM, Dr. Marcus Raichle wrote later in the excellent book chapter of "A Brief History of Human Functional Brain Mapping" (Raichle, 2000) that, "…the two groups (MGH and Minneapolis at the August 1991 meeting of SMRM) … realized for the first time who the competition was." Actually, I was not privy to any data brought to the meeting by the Minneapolis group and I remained unaware of the study on BOLD application for fMRI by Dr. Ogawa and Dr. Ugurbil's team until the Experimental Nuclear Magnetic Resonance (ENC) conference held in 1992, months after the 1991 SMRM meeting.

Under the research leadership of Dr. Bruce Rosen, there was well-found excitement in 1990–1991 at the MGH-NMR Center over Dr. Belliveau's pioneering fMRI experiments using an external contrast agent. But my personal preference was to look for intrinsic MR contrast if I could avoid administering external contrast agents. I had been interested in measuring perfusion with MR techniques for awhile. I had already obtained good perfusion result in animals with a bolus injection of H_2O^{17} in 1990 (Kwong et al., 1991). But H_2O^{17} is still an external contrast agent. At $1000 a cc, both the cost and the unclear health effect of mixing H_2O^{17} and normal water in human bodies limits the anticipated utility of H_2O^{17}. Under the free-wheeling and fertile intellectual environment structured and supported by Dr. Thomas Brady and Dr. Bruce Rosen at the MGH-NMR Center, I was given free rein and resources to test any wild ideas. At early 1991, I had knowledge on three other candidate MR techniques for perfusion measurement. I experimented with the popular MR diffusion technique (Le Bihan et al., 1988) based on intravoxel incoherent motion (IVIM) but was not able to provide a satisfactory interpretation of the MR results. Since imaging technology on diffusion and the models for vascular network continue to advance, IVIM remains an important research topic today (Koh et al., 2011). The second technique was arterial spin labeling (ASL) which I picked up from a poster given by Detre, Leigh and Koretsky (Detre et al., 1992; Williams et al., 1992) at the 9th Annual Meeting of SMRM at 1990. Based on my discussion with Dr. David Chesler who clarified for me the underlying idea of ASL designed to measure baseline resting perfusion, it occurred to me that ASL might also be a usable tool to measure change in brain perfusion, a change to be expected in any sensory or cognitive challenge. For the third perfusion candidate technique based on Keith Thulborn's work, I was hoping that the sensitivity of the gradient echo may be able to optimize the role of deoxyhemoglobin as a marker for blood signal change.

A hunt for diffusion work by Dr. LeBihan at the April 1991 Society of Magnetic Resonance Imaging (SMRI) meeting in Chicago led me fortuitously to a poster by Robert Turner, Denis Le Bihan, Chrit Moonen and Joe Frank. What caught my interest was the gradient echo

results from Dr. Turner's work. Dr. Turner provided the significant insight in associating perfusion with an overshoot in deoxyhemoglobin signal change in a hypoxia experiment with a cat. Dr. Turner's results on flow change played an important role in my future interpretation of the nature of the rising MR signal response in the upcoming visual imaging experiment.

While I had a hunch that MR signal based on deoxyhemogobin change might be usable to explore brain's sensory functions, it was a complete unknown at that time how large an MRI signal one could expect from intrinsic blood contrast in response to a simply sensory challenge, if anything could even be detected at all. I was able to duplicate Dr. Turner's respiratory challenge with rabbits and a dog. A single human breath-hold experiment yielded some interesting measurement in both gray and white matter. But a vast unknown gap was assumed to exist between the brain's physiological response to a hypoxic challenge and the brain's response to a sensory stimulus like vision. I walked into my first fMRI visual experiment with no assurance on what a simple sensory input could do to MR signal in the brain. When the experimental result turned out to be a rise in gradient echo signal at the visual cortex in response to the flickering light, Dr. Turner's results suggested that the MR signal rise due to deoxyhemoglobin change was associated with perfusion. With information shared by Dr. John Belliveau, I was also encouraged that the rise in gradient echo signal was consistent with the result of Fox et al (Fox and Raichle, 1986) which reported that blood oxygenation increased with heightened neural activity.

The May 9, 1991 experiment was surprisingly smooth and trouble free. I borrowed the visual stimulator of a pair of flickering goggles from Dr. Belliveau's Gd-DTPA fMRI experiments, the same goggles on loan from Dr. Peter Fox who used them in stimulation rate experiments in the early 1980's (Fox and Raichle, 1985). I consulted Dr. David Kennedy on where the V1 region was located in the brain so he could help me pick the proper single brain slice for imaging. The stimulus design was a block paradigm alternating a baseline **OFF** epoch with an **ON** epoch for the flickering visual input for a total of 70 time points. I ran a T2* weighted gradient echo EPI sequence as well as a T1 weighted inversion recovery spin echo EPI sequence. It was a surprise that the visual cortex "lit up" with MR signal change at the very first run of the gradient echo experiment. The inversion recovery spin echo result also demonstrated success the first time the flow-weighted sequence was run. Results obtained from subtracting the baseline epoch from the visual stimulation epoch were made available immediately after the image runs thanks to the homemade image data postprocessing software from Dr. Brigitte Poncelet. I associated the clearly observable signal change in the gradient echo responses with deoxyhemoglobin change and the change in the T1 weighted inversion recovery spin echo results with flow weighted responses. Development in later years pointed out the concern of BOLD contamination of flow weighted contrast and would proceed to more cleanly separate the mixture of flow and BOLD factors in pulsed ASL (Wong et al., 1997).

I had some recognition about the potential significance of my imaging outcome for brain imaging research. While I joked about "cold fusion" with colleagues on the results from May 9, my unspoken and immediate concern was reproducibility. Good visual cortex response was obtained from another volunteer on May 12. In days to follow the initial experiments, I moved to separate out credible hemodynamic effects from artifacts and learned to clarify the meaning of the MR signal change in response to functional stimulation. In that learning process, I received indispensable help and advice from Dr. John Belliveau, Dr. David Chesler, Dr. Robert Turner, Dr. Mark Cohen, Dr. Bruce Rosen and many other colleagues. Some of the co-investigators turned out to be exemplary imaging subjects demonstrating excellent visual responses in the brain, strengthening conveniently the confidence in the brain activation results of the visual regions. To demonstrate the general

usefulness of the BOLD and flow-weighted type of techniques in different cortical regions, I obtained later motor cortex activation with finger tapping.

The critical enabling technology of BOLD fMRI was the introduction of single-shot echo planar imaging (EPI). The long TR accessible to EPI vastly reduces unwanted in-flow signals and EPI's long readout enhances sensitivity to susceptibility contrast at 1.5T. The EPI MRI system at MGH, installed by Advanced NMR Systems (ANMR), was a powerful match with fMRI under the expert guidance of Dr. Mark Cohen and Dr. Robert Weisskoff. Single-shot EPI also laid bare any contribution of motion artifacts which became in principle manageable through judicious choice of motion correction algorithms. I followed up my EPI experiments quickly with short TR conventional spin-warp gradient echo (SPGR for the GE system) with the hope of reducing image distortion and to increase the spatial resolution of visual activation images. But with conventional gradient echo, I mostly got a number of extremely bright vessels at the cortical region due to T1 weighted inflow signal which is a bigger problem for higher magnetic field strength. The bright vessels were quite distracting and it was difficult to identify what was actually observable at the visual cortex upon stimulation. One of the biggest concerns in the use of the conventional gradient echo for fMRI research is also the increased difficulty in accounting for the contribution of motion artifacts to the finished image of a multi-shot MR sequence. While early efforts were made to reduce the T1 weighted inflow problem in order to utilize more the higher spatial resolution of the conventional gradient echo (Frahm et al., 1993), EPI became the productive workhorse by choice for fMRI applications.

The attempt to get the new fMRI results to the public ran into some unexpected headwind. My delivery of the "work in progress" abstract on the "movies of brain activation" to the 1991 SMRM conference was lost mysteriously in the mail. We had to settle for announcing the fMRI discovery in the paper presentation session by Bernice Hoppel on "regional blood oxygenation" and in the plenary session talk by Dr. Thomas Brady. Relieved that we finally got the novel and unambiguous results out to the public, colleagues and I then strove to writing a broad and comprehensive paper to showcase the new T2*-weighted and flow-weighted fMRI phenomenon. When we submitted the manuscript to Nature in October, we soon received a rejection with one of the reviewers commenting, "If the point of this paper is that MRI can be used to map the brain, this point has been made in the Science paper. If the point of this paper is that MRI can shed new light on the regulation of cerebral hemodynamics and metabolism by neural activity, I am not yet convinced."

The following comments raised by the same reviewer were helpful, "…do their studies confirm the PET observations of a rise in blood and tissue O2 content during focal neural activation or do they find a decrease in O2 content, suggesting an acute increase in O2 consumption." Had the manuscript not been rejected, we would have been able to reply with a model on how the rise in BOLD signal was related to cerebral blood flow (CBF), cerebral blood volume (CBV) and blood oxygen extraction (Kwong et al., 1992; Turner et al., 1991). Taking into consideration comments from those reviewers, our research team, with valuable input from Dr. Belliveau and other collaborators, expanded the scope and depth of our resubmission of the fMRI paper to PNAS in 1992. We stated (Kwong et al., 1992) that "our susceptibility-sensitive images show changes consistent with an increase in venous oxygenation…" and "…Our results independently confirm PET observations that activation-induced changes in blood flow and volume are accompanied by little or no increase in tissue oxygen consumption." Among the several new experiments organized for the PNAS paper, a point of interest was our incorporation of the stimulation rate experiment of Fox et al (Fox and Raichle, 1985) using the flickering goggles, highlighting the history of cooperation between the PET and fMRI communities. Overall, the thoughtful critiques from the early

reviewers contributed to making the published PNAS paper more useful to the field of functional brain imaging than the original submission to Nature.

Indeed, “shedding new light on the regulation of cerebral hemodynamics and metabolism by neural activity” is still an ongoing effort and cherished goal in the fMRI community. The perceptive demand of the reviewers remains relevant today.

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Highlights

- First fMRI experiments at MGH using intrinsic blood contrast
- Deoxyhemoglobin MR contrast; BOLD
- Flow-weighted MR contrast; Arterial spin labeling
- MR susceptibility contrast

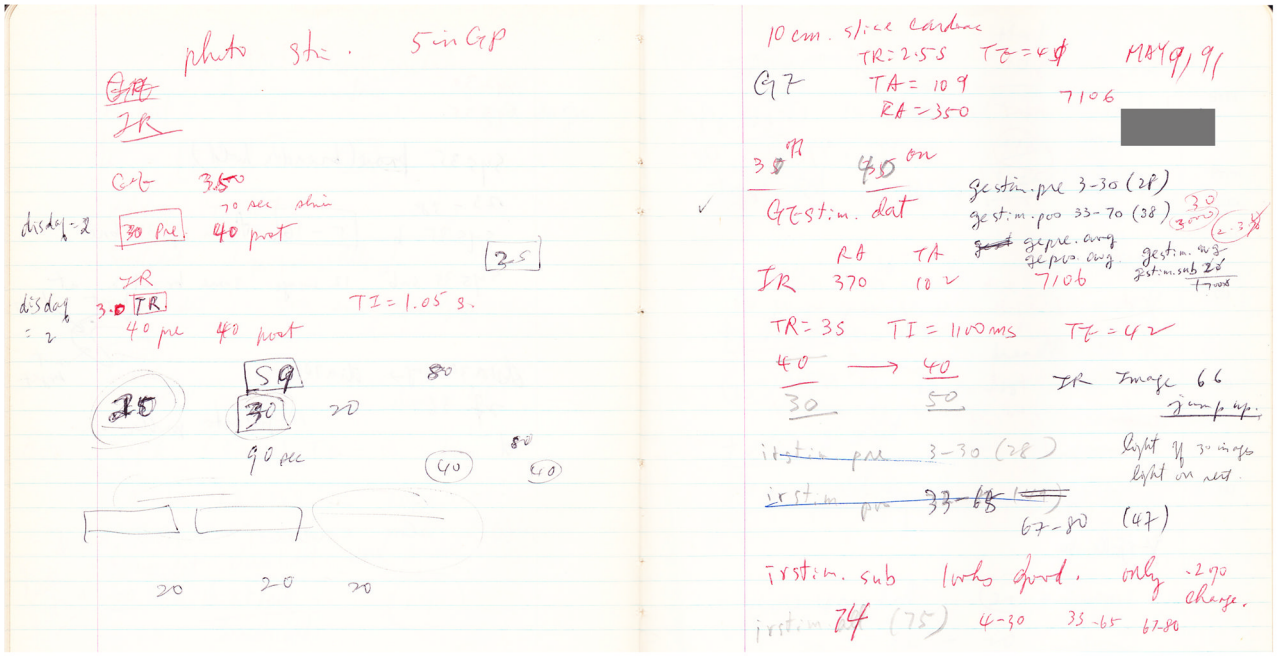

Fig. 1.

Reproduction of Kwong's log book pages recording the fMRI experiment on May 9, 1991. In this particular reproduction, the name of the imaging volunteer had been crossed out for privacy protection.