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Review

Twenty years of functional MRI: The science and the stories

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ABSTRACT

Since its inception over twenty years ago, the field of functional magnetic resonance imaging (fMRI) has grown in usage, sophistication, range of applications, and impact. After twenty years, it's useful to briefly look back as well as forward — to size up just how far we have come and speculate just how far we may go. This is an introduction to the special issue of "Twenty years of fMRI: the science and the stories." The one-hundred and three papers in this special issue highlight the major methodological developments and controversies of fMRI from a first person perspective over the past twenty years. The growth of this field is not just fascinating from a science and technology perspective, but also from a human perspective. Most who were fortunate enough to be part of this effort at the beginning, as well as those who jumped in along the way have their fair share of interesting stories consisting of top rate science as well as intense thought and effort, good or bad fortune, and some claim to a contribution. These stories are in the following papers, written by the current leaders in the field and the innovators throughout the twenty year history. The categories, designed to cover every aspect of the emergence and development of fMRI, include: pre-fMRI; the first BOLD brain activation results; developments in pulse sequences, imaging methods, and hardware for fMRI; methodological developments, issues, and mechanisms; new paradigm designs; education; and the future. Within this issue, we have a collage of overlapping, complementary, yet sometimes contradictory accounts of what happened during the breathtakingly diverse and intense development of this still growing field over the past twenty years.

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Introduction

Magnetic resonance imaging (MRI) came into common clinical use in about 1984 — only about six years before the first successful functional magnetic resonance imaging (fMRI) experiments were performed at Massachusetts General Hospital by Dr. John Belliveau. In these experiments, Dr. Belliveau and his colleagues obtained images collected sequentially over time using a technically challenging, hardware intensive, yet rapid and very stable pulse sequence called echo planar imaging (EPI) (Mansfield, 1977). Belliveau used an approach involving two sequential injections of Gadolinium during time series EPI data collection to create maps of cerebral blood volume before and during visual stimulation. The subtraction of these

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two blood volume maps (active minus rest) produced the now iconic image on the cover of the November 1, 1991 issue of Science (Belliveau et al., 1991). This Science cover image is also included within the cover of this special issue as well in a couple of articles from the MGH group (Cohen and Schmitt, 2012; Rosen and Savoy, 2012). This image revealed a localized increase blood volume in activated visual cortex, and, although the technique itself was essentially obsolete (for brain activation mapping) by the time it was published, it heralded in the beginning of the use of MRI to map human brain activation. Functional MRI research using *endogenous* contrast – that of blood susceptibility changes – was well underway since early 1991.

Sometime during the spring to summer of 1991, groups from Minnesota and MGH obtained the first successful fMRI results using endogenous blood oxygenation dependent (BOLD) contrast. The date that the MGH group reports that their first successful experiment occurred is May of 1991. The Minnesota group mentions "early summer" for theirs. It appears that MGH collected the first clear results slightly ahead of the Minnesota group. The stories of the first findings from these two groups are described in the special issue (Kwong, 2012; Ogawa, 2012; Ugurbil, 2012-a). Kwong, a talented experimentalist working on several methods to extract brain activity and metabolism information using MRI, and Ogawa, already having pioneered BOLD a couple of years prior and currently collaborating with Ugurbil, the steward of the first high field human magnets, were working independently toward the goal of using BOLD-based MRI to map human brain activity.

The first successful results from MGH were reported orally at the August 1991 Society of Magnetic Resonance (SMR) conference in San Francisco. Tom Brady gave his landmark plenary lecture showing a movie of human visual cortex lighting up (Brady, 1991). Shortly after this pivotal lecture and jaw dropping movie, several more groups jumped in. This next batch of successful results were produced, in approximate order, by my colleagues and I at the Medical College of Wisconsin (MCW) (Bandettini et al., 1992), Yale University (Blamire et al., 1992), the Göttingen group (Frahm et al., 1993), and the National Institutes of Health (NIH) (Turner et al., 1993). With regard to our work at MCW, the first successful results were obtained on Sept 14, 1991. Our group was fortunate enough to be the first to actually publish BOLD-based human brain activation results in a Communication in Magnetic Resonance in Medicine (Bandettini et al., 1992), followed a couple of weeks later by MGH (Kwong et al., 1992) and Minnesota collaborating with Bell Labs (Ogawa et al., 1992) in PNAS. Later, Blamire et al. (1992), Frahm et al. (1993), and Turner et al. (1993) published their results.

Each of these papers included a unique contribution. The MGH results, demonstrated visual cortex activation using BOLD contrast, but also included a novel MRI-based method to map perfusion changes associated with brain activation. In addition, they demonstrated a similar visual stimulation rate dependence as previously demonstrated with Positron Emission Tomography (PET) — helping to establish that this new technique was indeed sensitive to modulation in neuronal activity. The Minnesota results were obtained using a multi-shot imaging approach (difficult because of greater intrinsic instabilities in the time series), on a 4 Tesla scanner (the highest used on humans at the time). They were the first to show an echo time (TE) dependence of the brain activation-related BOLD response, thus further establishing that the effect was related to changes in transverse relaxation of blood. My results at MCW were unique in that they were the first to demonstrate BOLD-based left and right motor cortex activation using a whole brain RF coil and head gradient coil for EPI. Having measurements from the entire brain helped in further demonstrating that the signal changes were not an artifact of motion — which is not as easily discerned if only a surface coil is used. Our demonstration of independent left and right motor cortex activation further established the validity and spatial specificity of the technique. Blamire et al. was the first to demonstrate event related fMRI in the visual cortex. This last finding (event-related fMRI) went relatively unnoticed until this approach was re-discovered four years later in 1996 (Buckner et al., 1996b). Frahm et al., demonstrated fMRI at relatively high resolution at 1.5 T — also using a multi-shot approach. Lastly, Turner et al., compared high (4 T) and low (1.5 T) field strength effects, further establishing that it is a BOLD effect arising from changes in the bulk susceptibility of blood.

Functional MRI, though newly discovered, was relatively fast, non-invasive, and, importantly, *it just worked* — amazingly well. Even though the underlying relationships between changes in brain activation and changes in BOLD contrast-weighted MRI signal are still debated, it's clear that the method has proven itself more robust, reliable, and information-rich than most originally anticipated. We are still being surprised by the information that's there. I can't help but mention a recent paper showing that with simple tasks and unconstrained models, activation appears to be occurring practically *everywhere* in the brain (Gonzalez-Castillo et al., 2012) — each region having a uniquely identifiable time course.

With the fMRI results in the very early nineties, MRI itself took on an entirely new direction. Rather than MRI providing only anatomic and some basic physiologic information, it now could produce dynamic brain activation maps quickly, non-invasively, and with relatively high resolution. Many MRI technicians, industry engineers, marketing people, radiologists, scientists and others of the MRI establishment were nonplussed as researchers started having healthy volunteers, in the name of brain activation, doing all kinds of odd things in the magnet other than simply lying perfectly still with eyes closed — then producing highly processed and wildly colored maps rather than the standard gray scale. A revolution had begun. We could now look into the human brain as never before — *and we were leveraging mostly established technology to do it.*

Prior to 1991, the properties of hemoglobin were well-understood. Sixty years prior, Linus Pauling reported that the magnetic susceptibility of hemoglobin changed as a function of whether it was bound to oxygen or not (Pauling and Coryell, 1936). In the early 80s, Thulborn et al. (Thulborn et al., 1982) and others (Brindle et al., 1979; Brooks and Di Chiro, 1987; Fabry and San George, 1983; Gomori et al., 1987; Terrier et al., 1989) discovered that the transverse relaxation of blood changed with blood oxygen saturation. In the mean time, Fox et al. demonstrated using PET that, with activation, oxygen extraction decreased, implying an increase in blood oxygenation (Fox and Raichle, 1986), and thus, five years before the first fMRI results were reported, predicted that BOLD signal should increase with activation. Still, most who understood blood magnetic susceptibility in the context of MRI did not typically think about brain activation and also did not intuit that physiologically normal brain activation related oxygenation related changes in blood susceptibility would be enough to change the MRI signal.

Ogawa took Thulborn's work further, demonstrating in vivo that changes in blood oxygenation altered T2 and T2*-weighted MRI signal (Ogawa et al., 1990a). Turner et al. was the first to capture the EPI time series of blood oxygenation changes in cat brains during a global oxygenation stress (Turner et al., 1991). In the mean time, other methods showed promise for imaging brain activation related changes. Denis Le Bihan had developed Intravoxel Incoherent Motion (IVIM) as a method in which diffusion gradients are used to sensitize the signal to capillary perfusion (Le Bihan et al., 1987). IVIM, while raising the field's awareness of the potentially rich information contained in the MRI signal, ended up being too insensitive to capillary perfusion and too sensitive to cerebral spinal fluid (CSF) pulsation at the time (Kwong et al., 1991). The group at Pittsburgh, directed by Alan Koretsky, was developing a method for non-invasively mapping baseline perfusion, and, potentially changes in perfusion associated with activation (Williams et al., 1992). This technique has also seen some success in the past twenty years due to more precise brain activation localization, baseline information, time course

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