2016 Summer Neuroimaging Course

#	Day	Date	Room	Time	Topic	Lecturer
1	Tuesday	5/31/16	40	2:00 PM	Introduction to Course & A history of fMRI and Neuroimaging	Peter Bandettini
2	Tuesday	5/31/16	40	3:00 PM	Functional MRI contrast and the limits of spatial and temporal resolution	Peter Bandettini
3	Monday	6/6/16	49	2:00 PM	fMRI Paradigm Designs and Processing Methods	Peter Bandettini
4	Wednesday	6/8/16	40	2:00 PM	Overview of tradeoffs in fMRI acquisition	Jen Evans
5	Friday	6/10/16	40	2:00 PM	Basics of MRI and how to identify artifacts	Vinai Roopchansingh
6	Monday	6/13/16	49	2:00 PM	Advanced MRI and fMRI Acquisition Methods	Andy Debyshire
7	Wednesday	6/15/16	40	2:00 PM	Resting State fMRI	Catie Chang
8	Friday	6/17/16	49	2:00 PM	What's neuronal and what's not in fMRI	Dan Handwerker
9	Monday	6/20/16	40	2:00 PM	Dynamic Resting State fMRI	Javier Gonzalez-Castillo
10	Wednesday	6/22/16	40	2:00 PM	Multi-echo EPI for task-based and resting-state fMRI	Javier Gonzalez-Castillo
11	Friday	6/24/16	40	2:00 PM	Perfusion Imaging	Lalith Talagala
12	Monday	6/27/16	40	2:00 PM	Neuromodulation methods	Bruce Luber
13	Wednesday	6/29/16	40	2:00 PM	T1 Contrast, MPRAGE and MT	Peter van Gelderen
14	Friday	7/1/16	40	2:00 PM	Approaches to functional activity mapping during natural viewing	Brian Russ
15	Wednesday	7/6/16	40	2:00 PM	Anatomical and Functional Neuroimaging in Animal Models	Afonso Silva
16	Friday	7/8/16	40	2:00 PM	Multivariate pattern analysis and brain decoding	Martin Hebart
17	Monday	7/11/16	49	2:00 PM	fMRI Methods that have never quite caught on	Peter Bandettini
18	Wednesday	7/13/16	49	3:00 PM	Neuromodulation applications	Sarah Lisanby
19	Friday	7/15/16	40	2:00 PM	Quantitative MRI	Govind Bhagavatheeshwaran
20	Monday	7/18/16	35A/640	2:00 PM	Studying CNS diseases with advanced MRI	Pascal Sati
21	Wednesday	7/20/16	40	2:00 PM	fMRI and MRI at the NIH	Sean Marrett
22	Friday	7/22/16	40	2:00 PM	Imaging Stroke and Traumatic Brain Injury	Lawrence Latour
23	Monday	7/25/16	10/2/30	2:00 PM	AFNI plus SUMA: analyzing your data	Bob Cox
24	Wednesday	7/27/16	40	2:00 PM	Statistics of fMRI	Gang Chen
25	Friday	7/29/16	40	2:00 PM	The AFNI - based Functional and Anatomical Connectivity Platform	Paul Taylor
26	Monday	8/1/16	40	2:00 PM	fMRI Data Sharing	Adam Thomas
27	Wednesday	8/3/16	35A	2:00 PM	Human Spectroscopy	Jun Shen
28	Friday	8/5/16	49	2:00 PM	Positron Emission Tomography (PET)	Bob Innis
29	Monday	8/8/16	40	2:00 PM	Mediation analysis for fMRI based pain assessment	Lauren Atlas
30	Wednesday	8/10/16	49	2:00 PM	Magnetoencephalography (MEG)	Richard Coppola
31	Friday	8/12/16	49	2:00 PM	What actually is connectivity? How to measure? How to quantify?	Panel / Steve Gotts
32	Monday	8/15/16	40	2:00 PM	Multi-modal imaging, EEG-fMRI	Silvina Horovitz
33	Wednesday	8/17/16	49	2:00 PM	Diffusion MRI	Joelle Sarlls
34	Friday	8/19/16	40	2:00 PM	fMRI of Mood Disorders	Allison Nugent
35	Monday	8/22/16	40	2:00 PM	fMRI of Development	Danny Pine
36	Wednesday	8/24/16	40	2:00 PM	What you can and cannot do with diffusion MRI	Carlo Pierpaoli
37	Friday	8/26/16	40	2:00 PM	Non-Human Primate fMRI and everything it has to offer	David Leopold
38	Monday	8/29/16	40	2:00 PM	Clinical applications of fMRI	Peter Bandettini
39	Wednesday	8/31/16	40	2:00 PM	fMRI of the individual - and the future of fMRI	Panel / Peter Bandettini

A Brief History of Neuroimaging & fMRI

Peter A. Bandettini, Ph.D.

Section on Functional Imaging Methods

Laboratory of Brain and Cognition

http://fim.nimh.nih.gov

&

Functional MRI Facility

http://fmrif.nimh.nih.gov

Brief History of Brain Imaging

1. **Lesion-based Mapping.**
2. **Anatomic Imaging.**
3. **Hemodynamic and Metabolic Imaging.**
4. **Electrophysiologic Imaging**
5. **Functional MRI**

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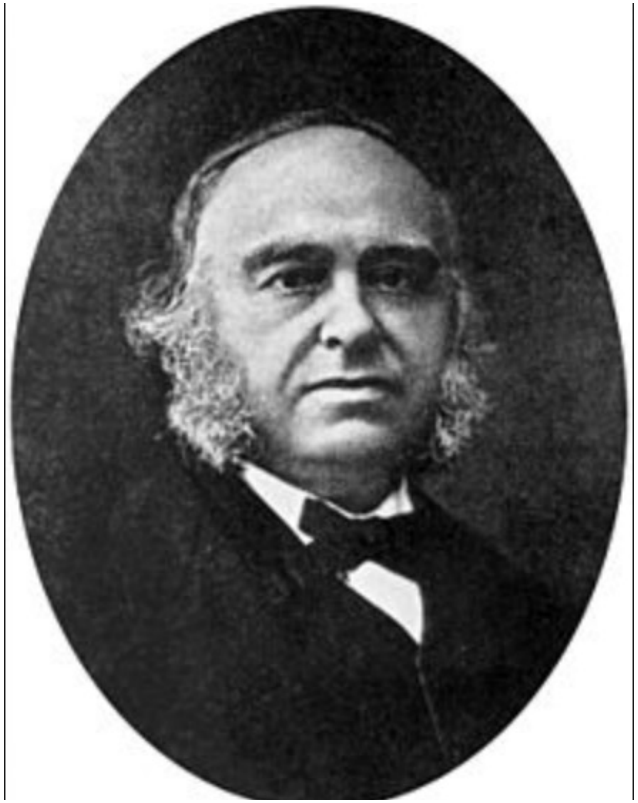
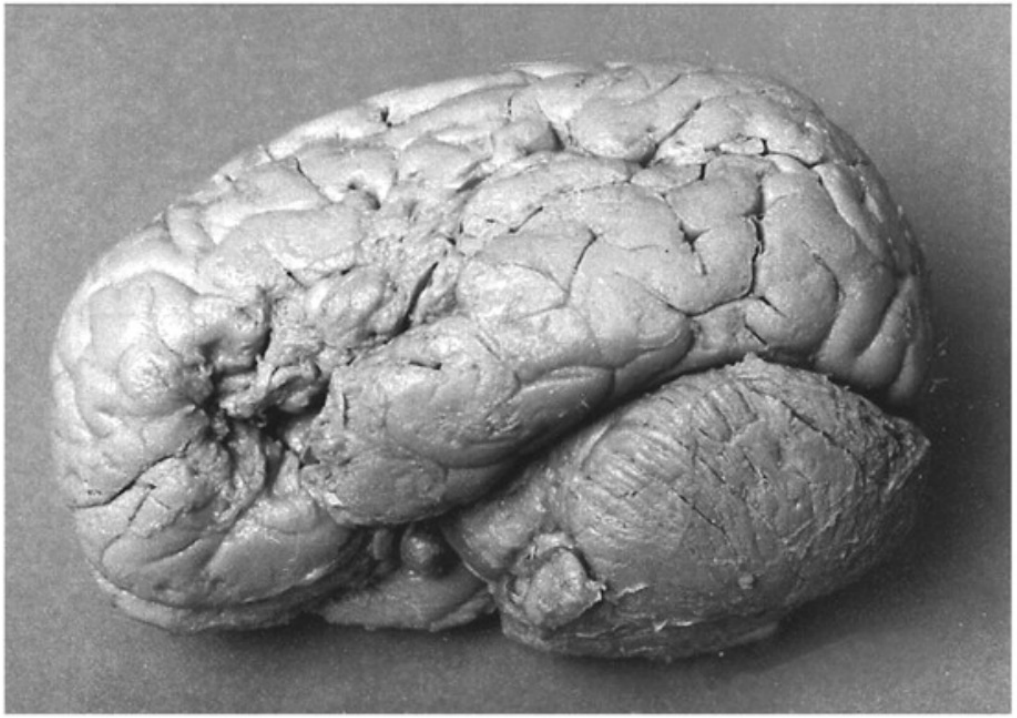
1861 Paul Broca:

His patient, Leborgne, could only produce "tan."

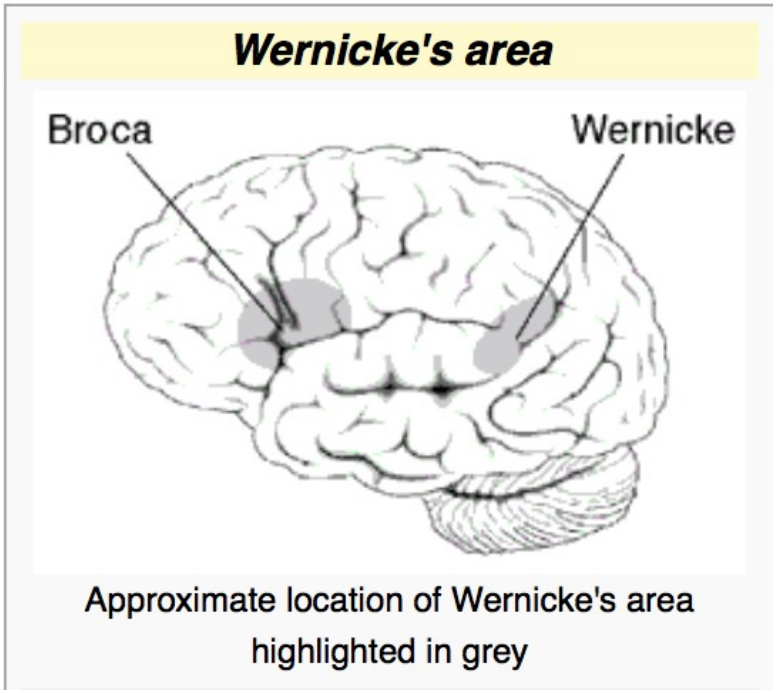




1874: Carl Wernicke

His patients could not understand or produce meaningful speech but could articulate words.

Carl Wernicke



Approximate location of Wernicke's area highlighted in grey

Aphasias

- Broca's Aphasia: disturbance in speech production, caused by damage to Broca's area
  - http://www.youtube.com/watch?v=f2IiMEbMnPM
    - Agrammaticism
    - Anomia
    - Difficulty with articulation
- Wernicke's Aphasia: disturbance in speech comprehension, caused by damage to Wernicke's area
  - http://www.youtube.com/watch?v=aVhYN7NTIKU&feature=related
    - Disruption in recognition of spoken words
    - Disruption in comprehension of the meaning of words
    - Inability to convert thought into words

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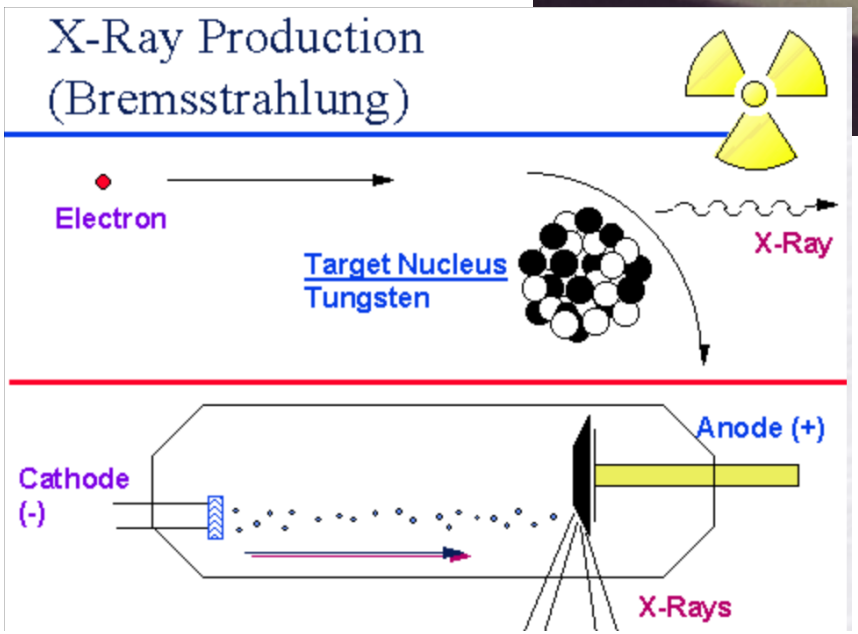
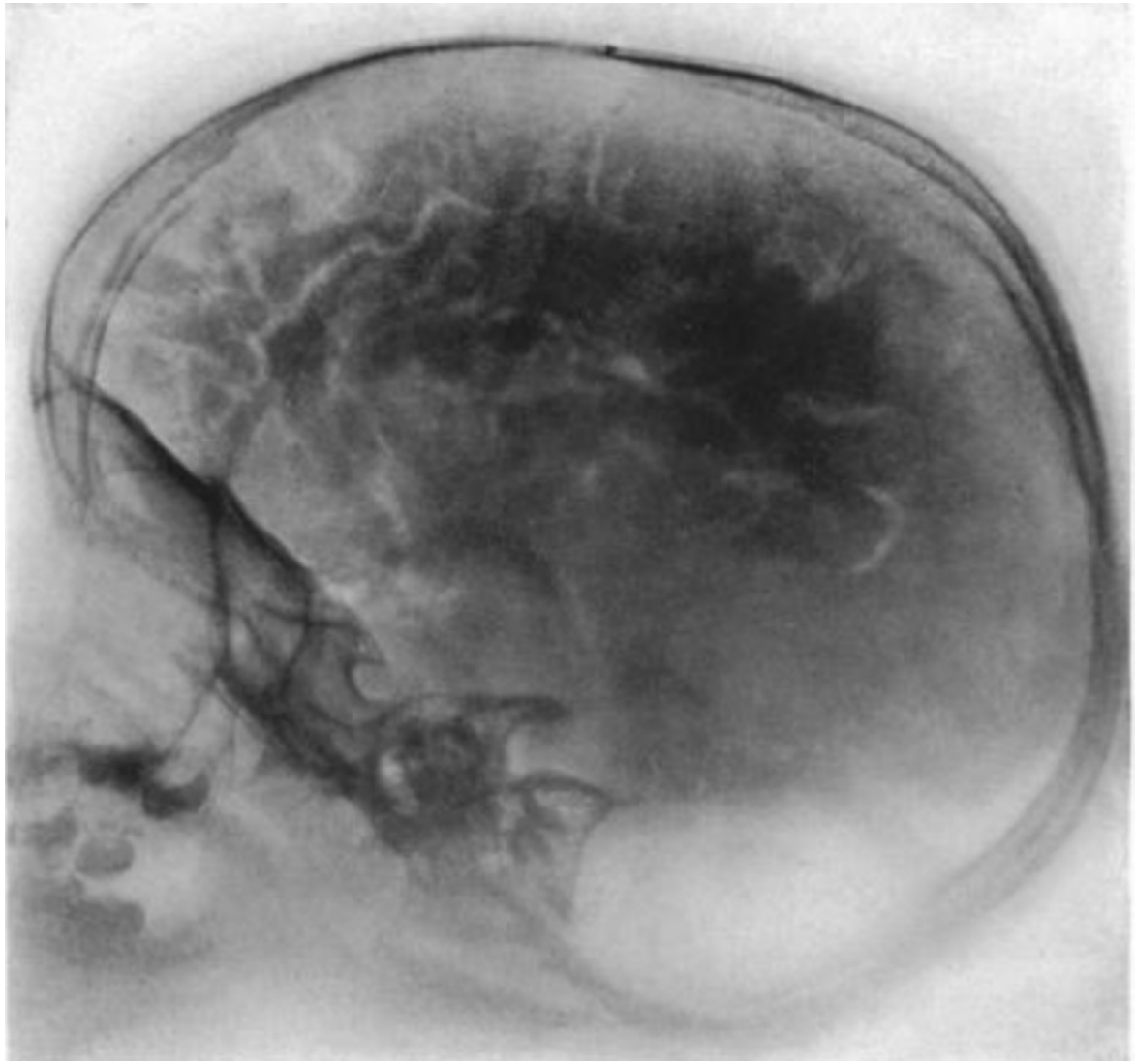
1895: Roentgen discovers x-rays and their utility



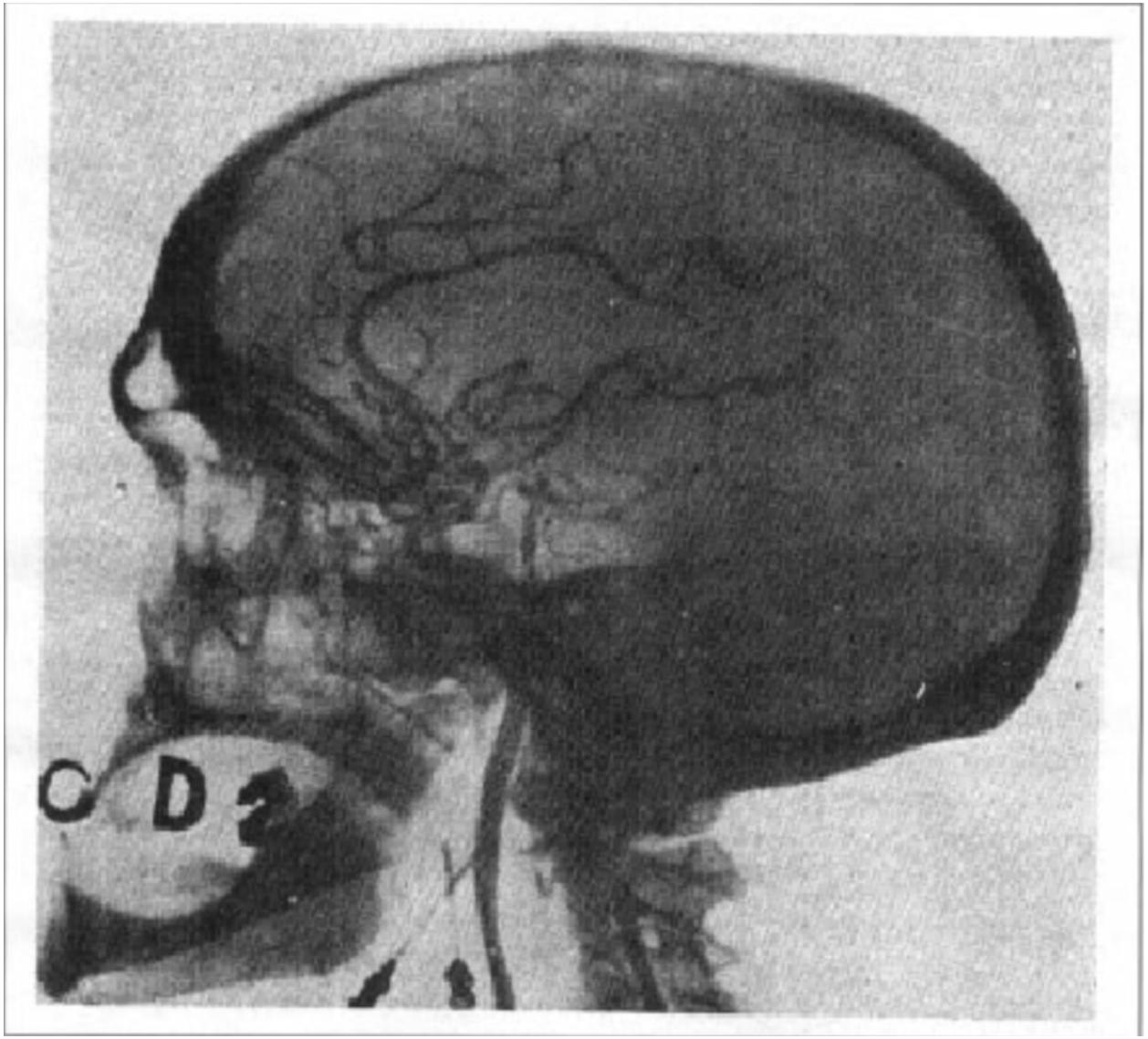
Crooke's tube

Early 1900's: Pneumoencephalography

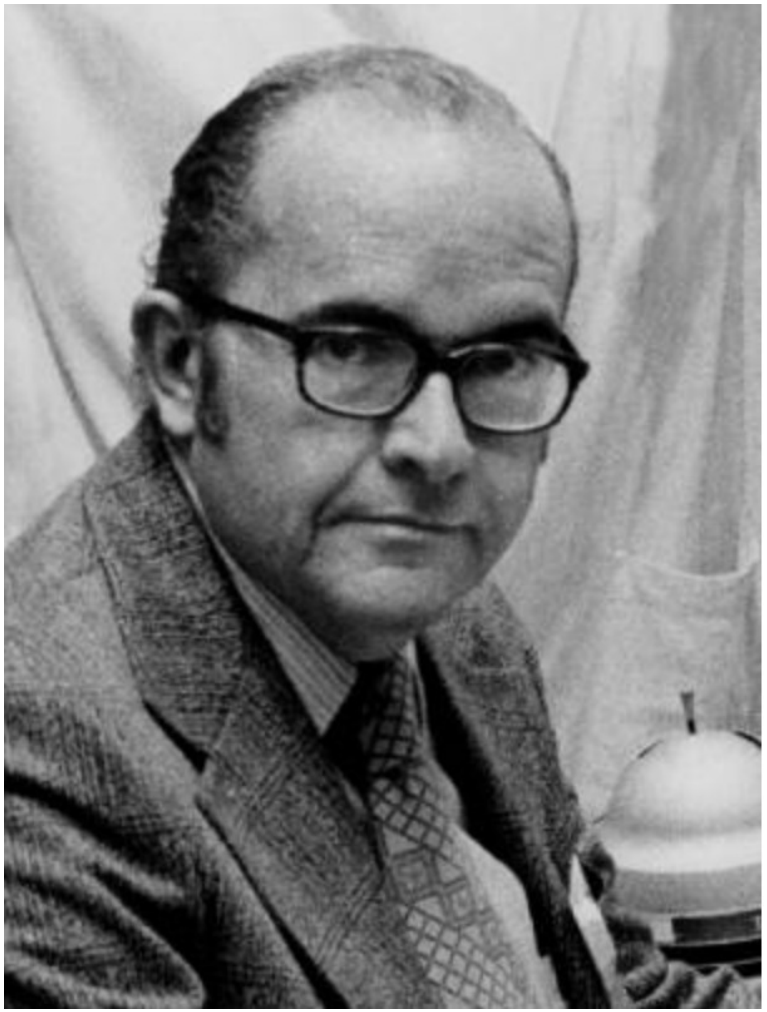
CSF drained from the brain to enhance contrast in x-rays



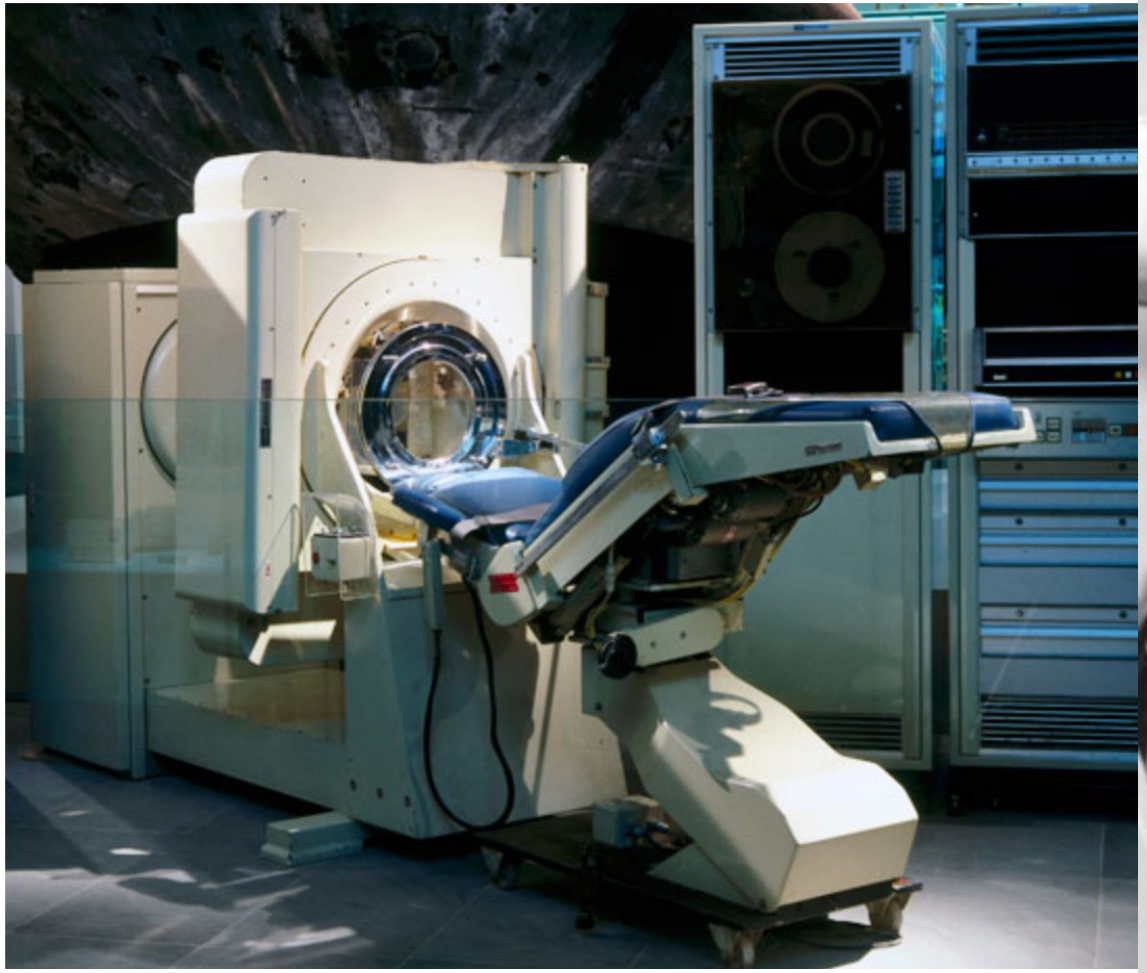
1927: Antonio Egas Moniz – first Arteriogram

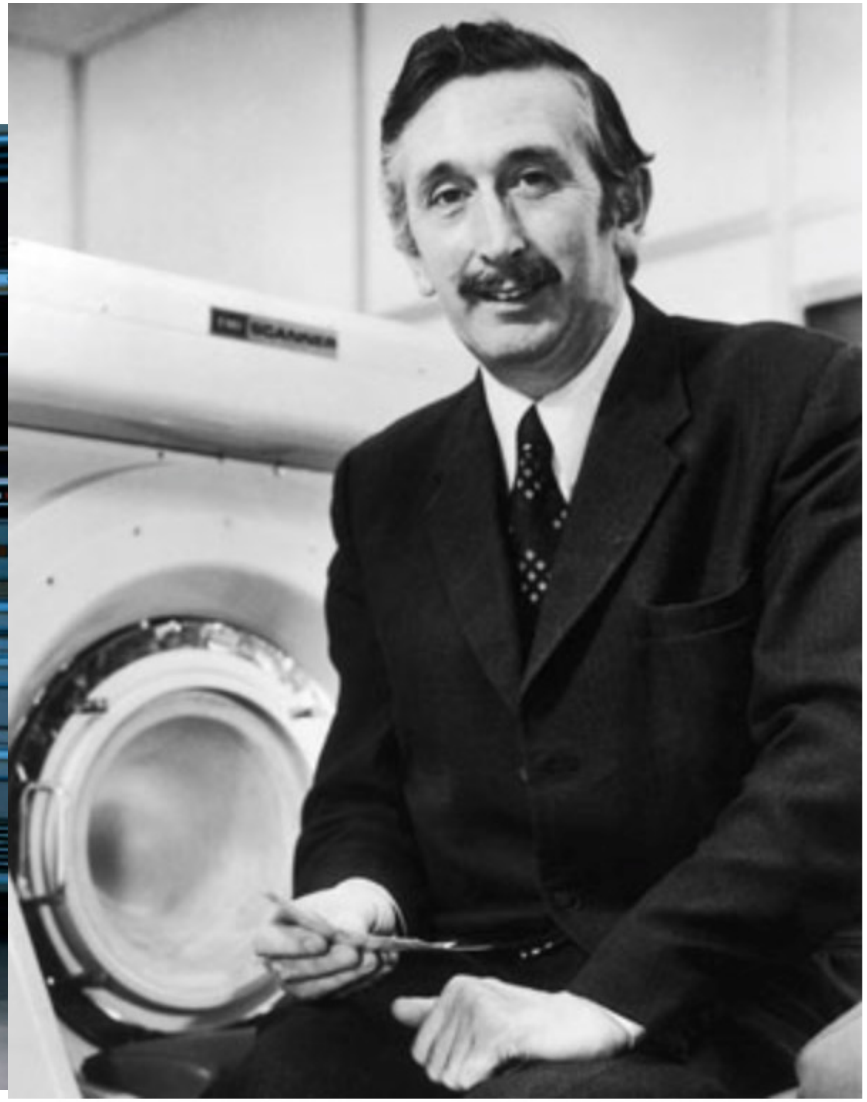


1960, William Oldendorf patented an electronically based device that could capture image slices continuously through a solid object.



1971: Hounsfield implemented the first CT scanner





Godfrey Hounsfield received the 1979 Nobel Prize in Medicine for his work in the development of computer assisted tomography (CAT) scanning.

MRI: Magnetic Resonance Imaging

Sir Peter Mansfield and Paul Lauterbur, Winners of the Nobel Prize for Medicine, 2003

Lauterbur's Contribution: Projectional NMR Tomography

Paul Lauterbur (1909-2007), a chemist working at the State University of New York at Stony Brook, published the first true MR image in *Nature* in March, 1973. His experimental setup involved two 1-mm-diameter tubes filled with water placed in an 1.4T magnet. Applying magnetic field gradients rotated successively by 45°, he was able to obtain four different 1-dimensional projections of the NMR signal. These data were then mathematically "back-projected" to form a 2-dimensional tomographic image. Because the result depended on the combined effects of two magnetic fields, Lauterbur named his technique "***zeugmatography***" after the Greek word, *zeugma*, meaning "that which is used for joining." Shortly thereafter, Lauterbur produced crude images of his first living subject: a tiny clam.

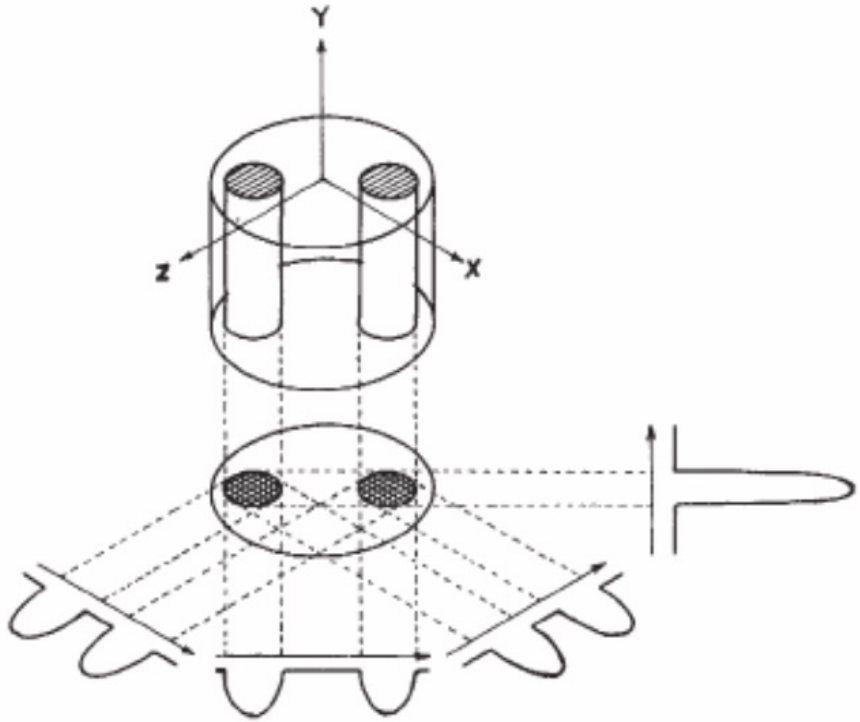
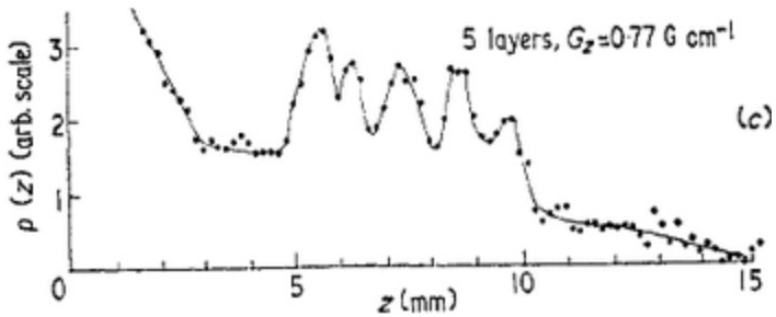


Fig. 1 Relationship between a three-dimensional object, its two-dimensional projection along the Y-axis, and four one-dimensional projections at 45° intervals in the XZ-plane. The arrows indicate the gradient directions.

Fig. 2 Proton nuclear magnetic resonance zeugmatogram of the object described in the text, using four relative orientations of object and gradients as diagrammed in Fig. 1.

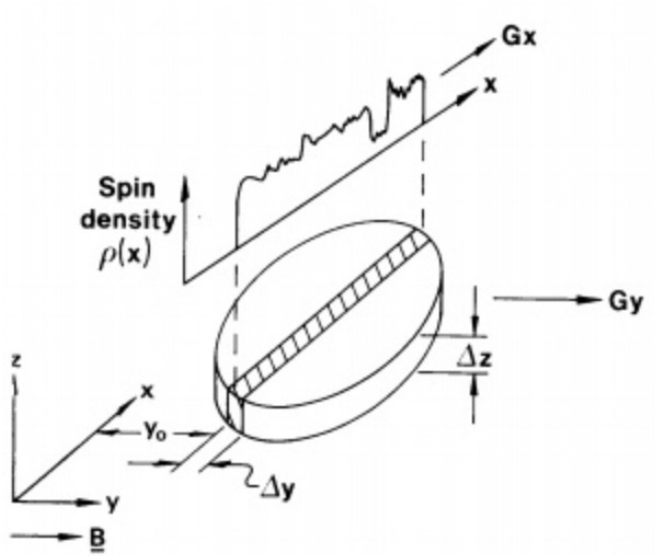
Mansfield's Contribution: Use of a field gradient for slice selection



From Mansfield (1973). Five peaks corresponding to five stacked blocks of solid camphor.

Also in 1973, ***Peter Mansfield*** (b. 1933), a physicist working at the University of Nottingham, demonstrated how a linear field gradient could be used to localize the NMR signal on a slice-by-slice basis. Mansfield's experimental setup involved stacking multiple 1-mm-thick sheets of solid camphor into the bore of an NMR spectrometer. Applying a magnetic field gradient perpendicular to the sheets, Mansfield measured the transient NMR signal response to an applied RF-pulse. Interference peaks similar to those seen in x-ray diffraction were observed, which when inverse Fourier transformed revealed discrete layers of the camphor sample.

Later in the decade, Mansfield and his collaborator, Andrew Maudsley, further refined this method into a line-scan technique, producing the first image of a human body part, a finger, in 1977.



Line-scan technique, selectively irradiating a narrow strip with an isolated slice of magnetization.

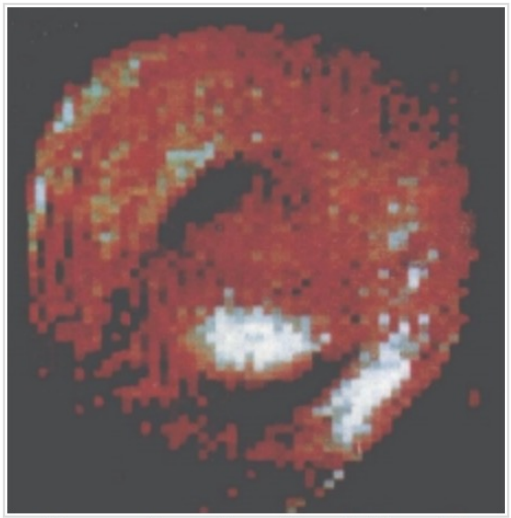
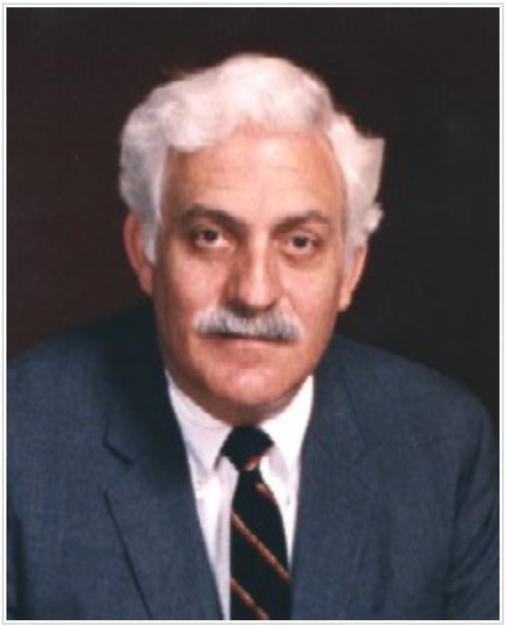


Image of human finger from Mansfield and Maudsley (1977) using line-scan technique obtained at 0.35T in 23 minutes. The white oval is marrow within the phalanx and the dark bands are tendons.

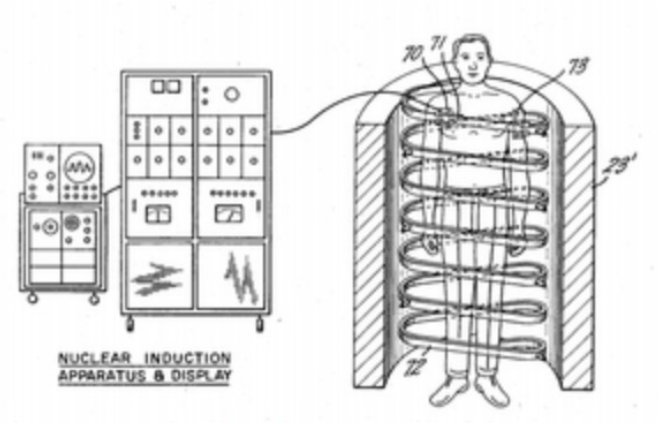
Damadian's Contribution: Vision of a human-sized scanner to detect disease



Raymond V. Damadian

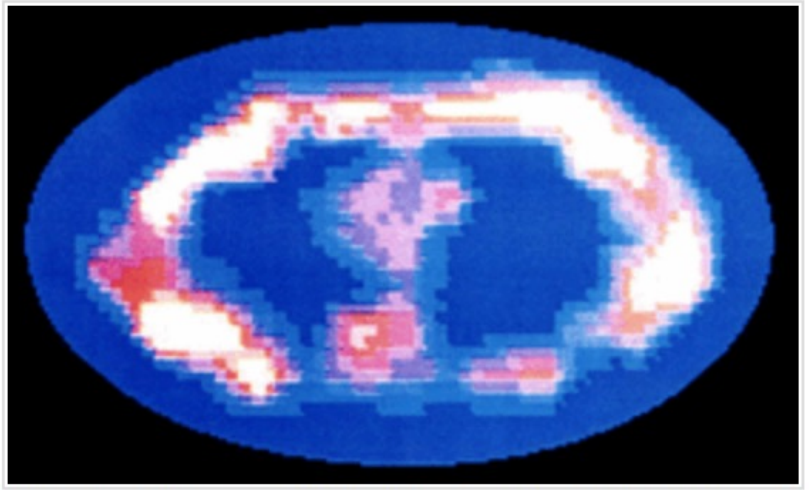
Assistant Larry Minkoff in Indomitable

While Lauterbur and Mansfield were basic scientists, ***Raymond V. Damadian*** (b. 1936) was a physician, an Associate Professor of Medicine at the State University of New York - Brooklyn (Downstate). He looked at NMR from a different and original perspective — as a phenomenon that might be used to probe the body and diagnose human disease. In one of his landmark early papers (*Science*, 1971) Damadian demonstrated that cancer cells had longer T1 and T2 values than normal cells. In 1972 he filed a US patent application for an apparatus and method to detect cancer in tissue. Although the details of exactly how this 'apparatus" would produce images were not included in the application, Damadian and his team set out to build such a device which was named "***Indomitable***." By mid-summer, 1977, the first whole-body MR images were being produced, including the famous one shown below of his assistant's chest.



Damadian's 1972 patent application

Damadian used a "sensitive point" method for spatial localization of the NMR signal. This was based on a saddle-shaped magnetic field where only a small volume at the center matched the resonance frequency of the RF pulse. The patient's body was physically moved in a rectangular pattern until signals from all pixels were obtained.



First whole body image (Minkoff's chest), obtained July, 1977. It required nearly 5 hours to produce.

Damadian called his imaging method "field-focused NMR" or FONAR. This became the name of his company, the first to manufacture clinical MR scanners commercially. It was soon recognized that the field-focused method was far too slow and clumsy for routine clinical imaging, and so it was abandoned in favor of the methods of Lauterbur and Mansfield in subsequent versions of the scanner.

When the 2003 Nobel Prizes for Medicine were announced, Damadian considered it a personal injustice that he was excluded. He placed full-page ads in several large world newspapers urging the Nobel committee to change its mind. The decision stood.

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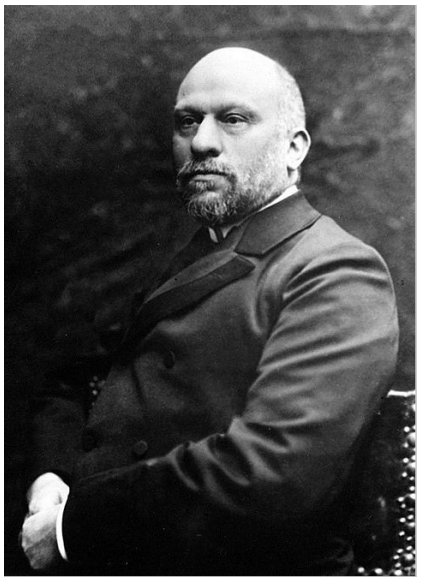
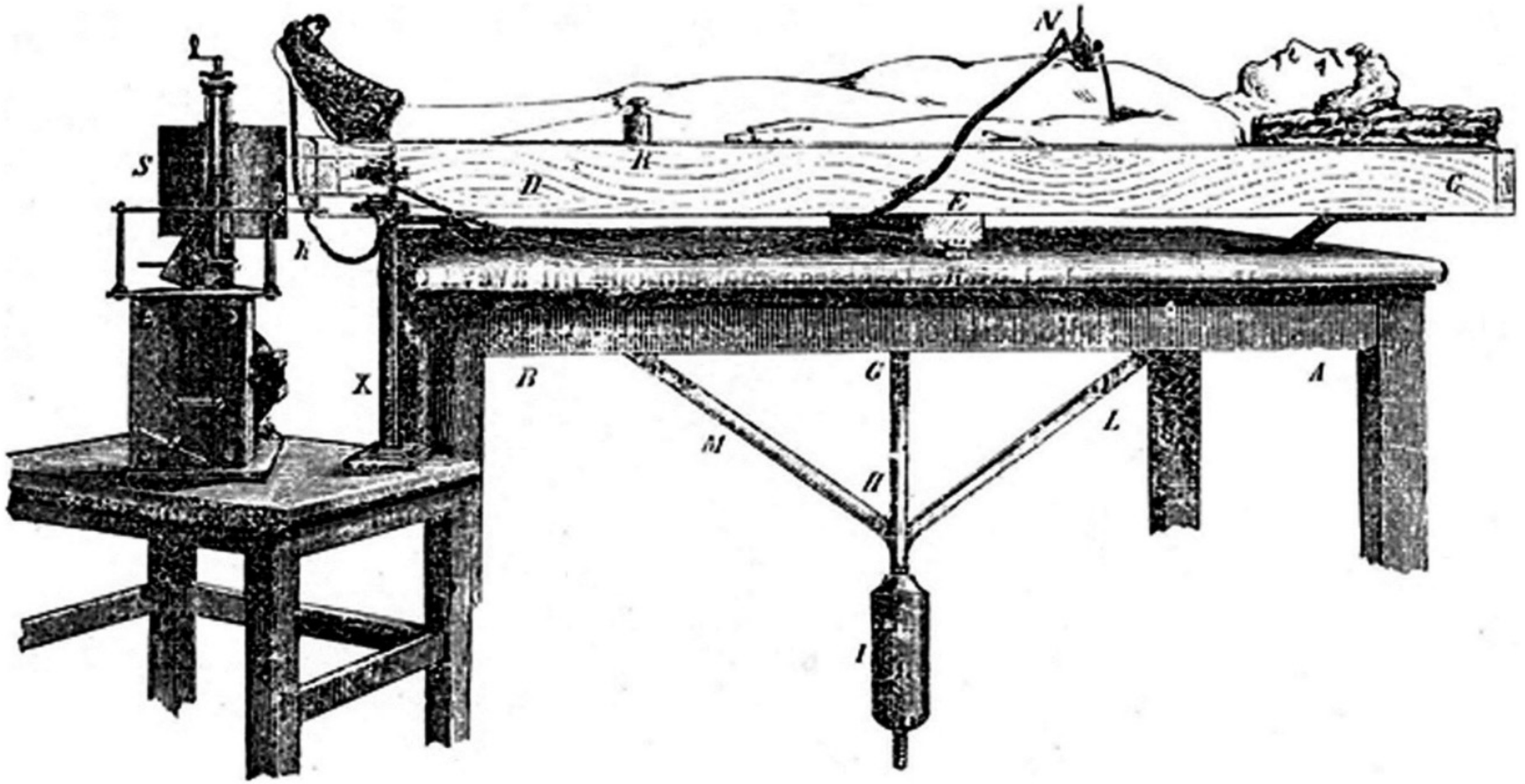
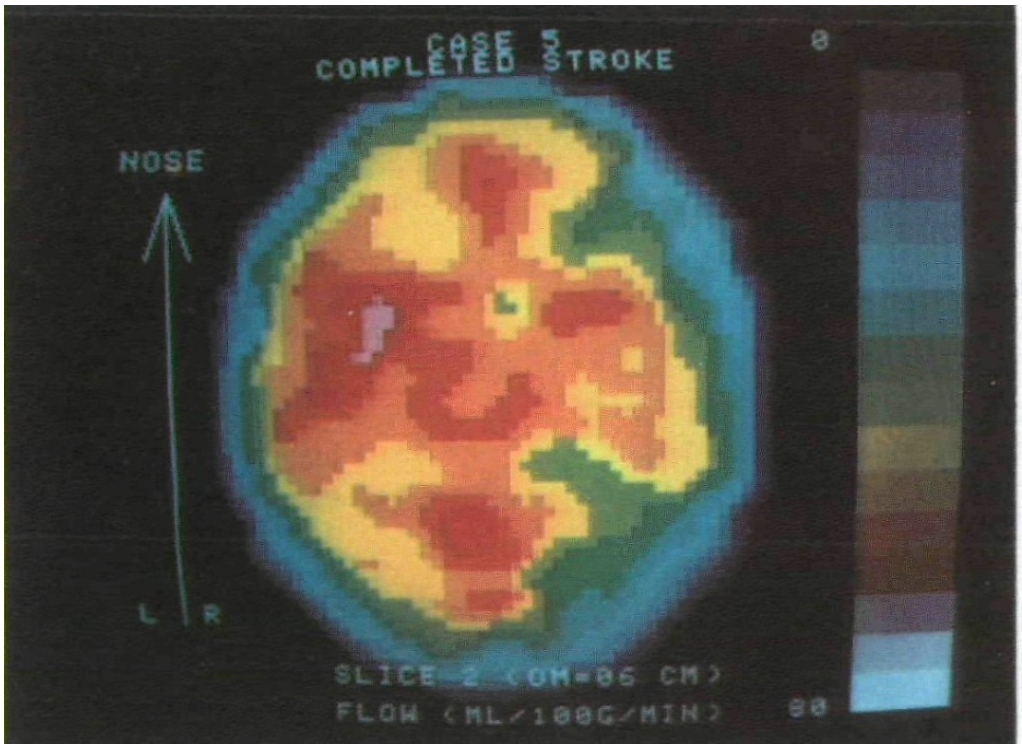
1880's: Angelo Mosso's balance

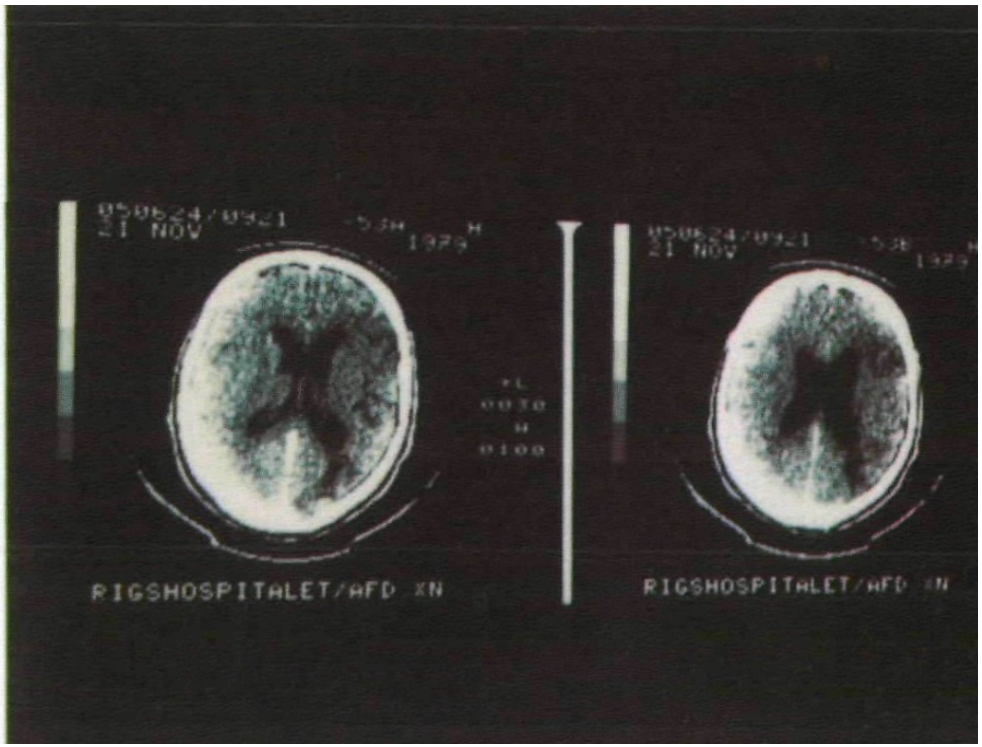




1960's to 70's: Xenon inhalation

Niels A. Lassen, David H. Ingvar, Erik Skinhøj, "Brain Function and Blood Flow", *Scientific American, 239(4):50-59, 1978 October*





Isotope	half-life (min)	Maximum positron energy (MeV)	Positron range in water (FWHM in mm)	Production method
^{11}C	20.3	0.96	1.1	cyclotron
^{13}N	9.97	1.19	1.4	cyclotron
^{15}O	2.03	1.70	1.5	cyclotron
^{18}F	109.8	0.64	1.0	cyclotron
^{68}Ga	67.8	1.89	1.7	generator
^{82}Rb	1.26	3.15	1.7	generator

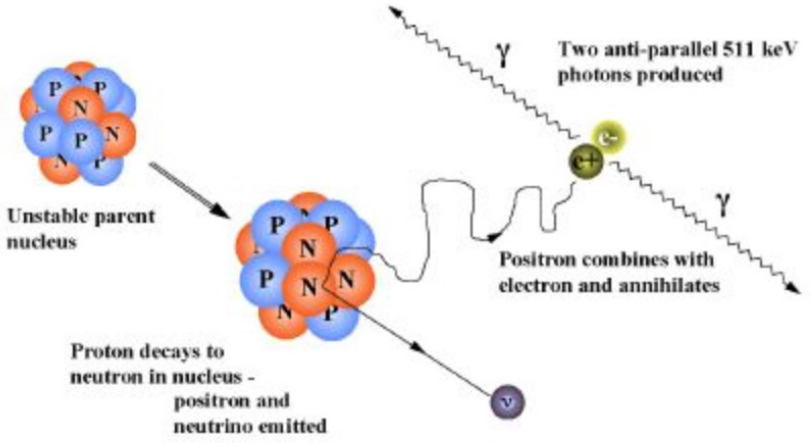


Figure 1. Positron emission and annihilation.

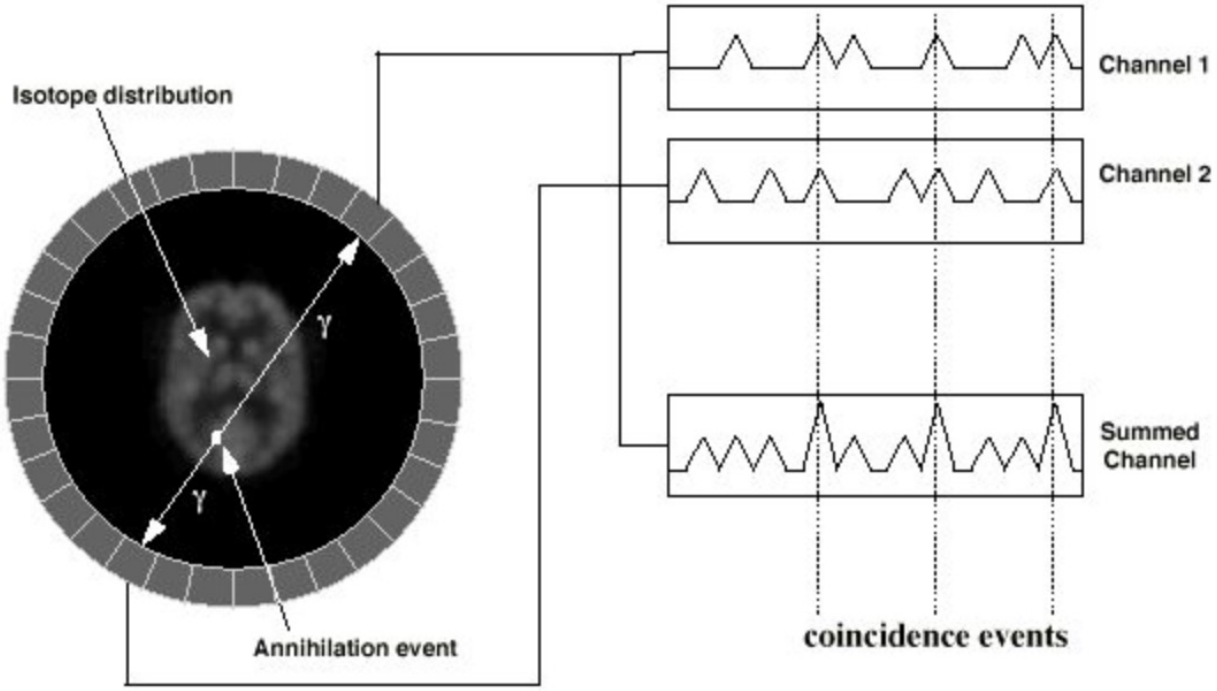
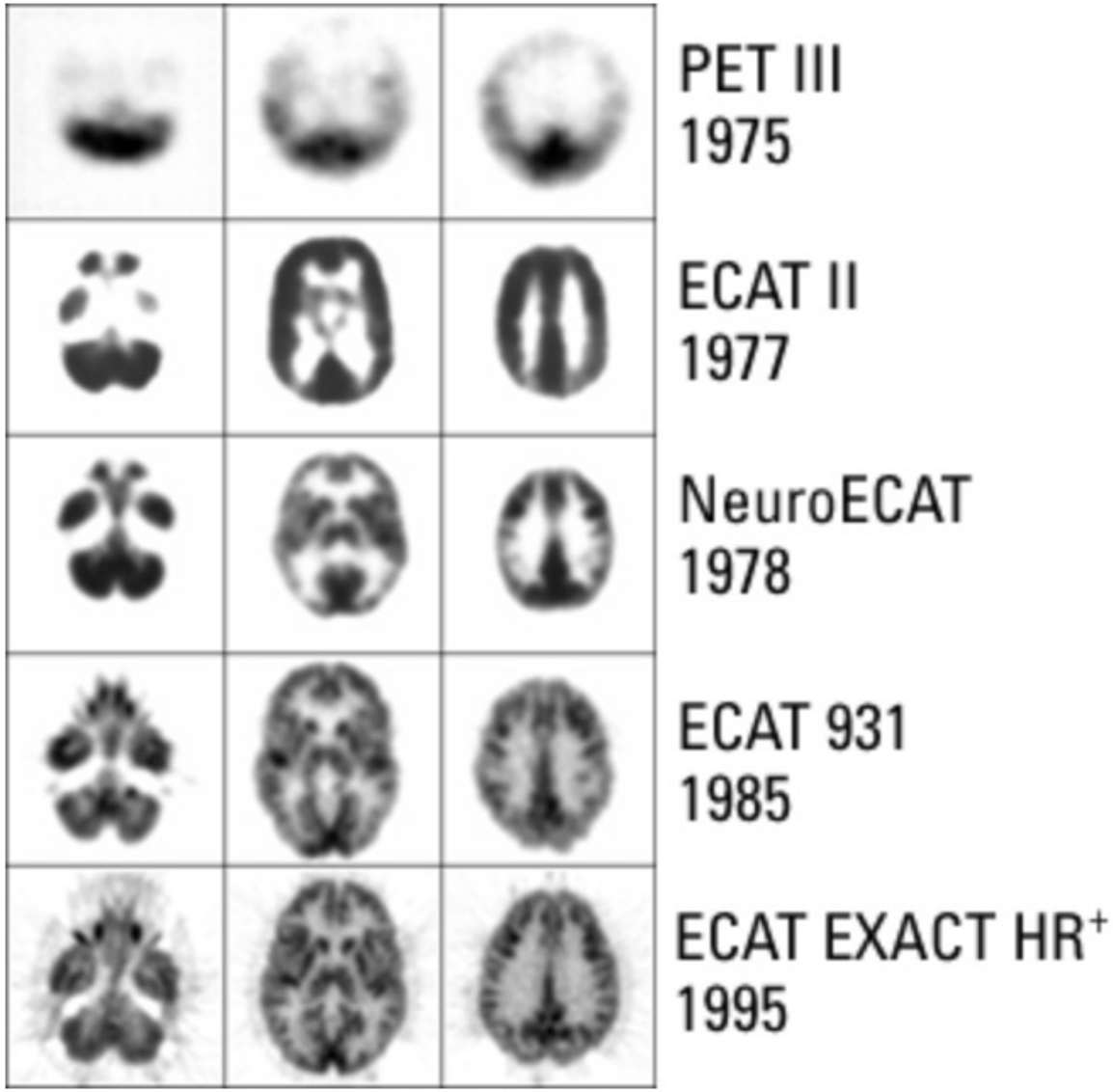
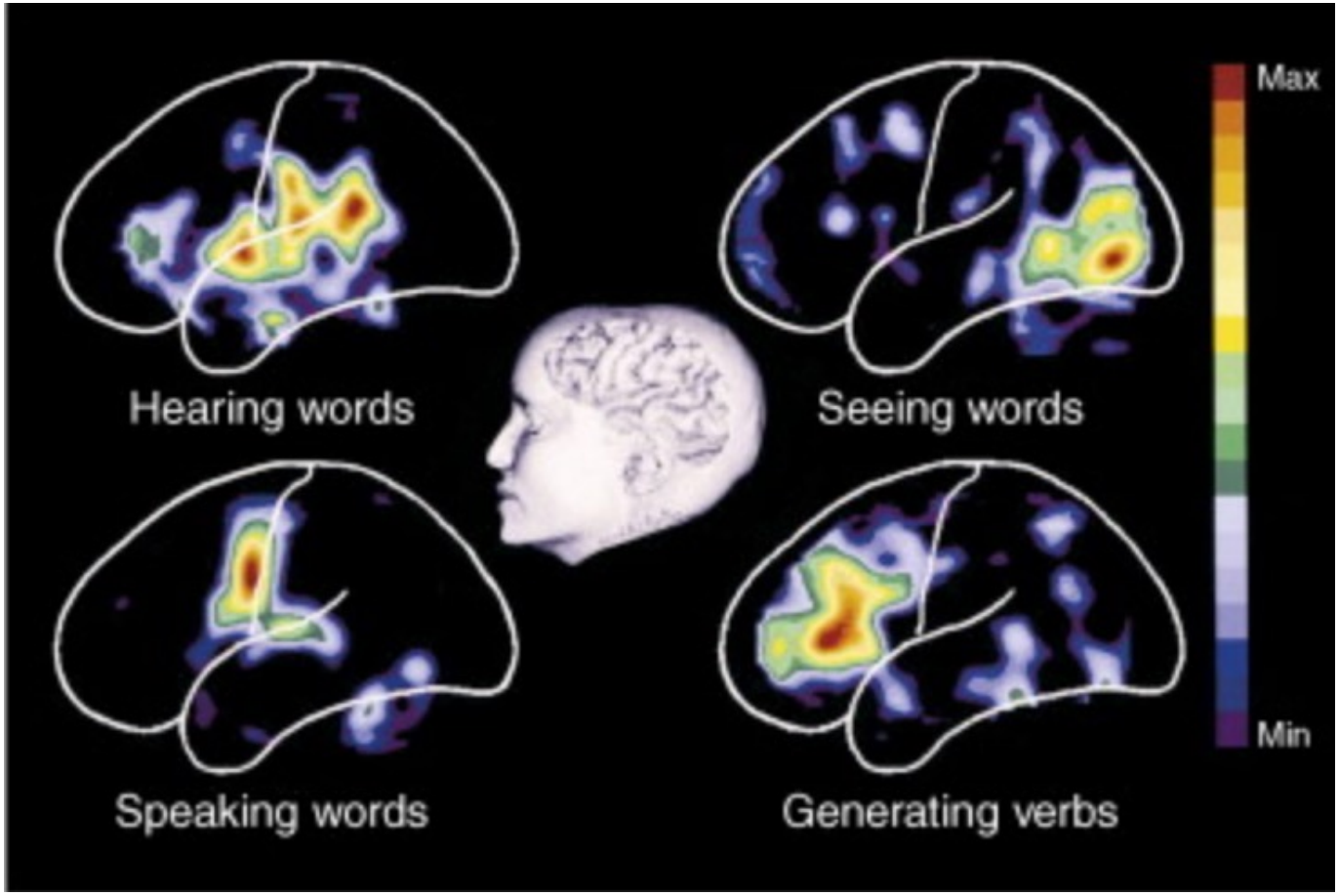


Figure 2. Coincidence detection in a PET camera.

1973: Michael Ter-Pogossian, Edward Hoffman, and Micahale Phelps - First Human PET scanner





Positron emission tomographic studies of the cortical anatomy of single-word processing. Petersen, S.E. et al. Nature. 1988; 331: 585–589

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From the electrical nature of brain signals …

1875: R.C. measured currents inbetween the cortical surface and the skull, in dogs and monkeys

Richard Caton
1842 - 1926

1924: H.B. first EEG in humans, description of alpha and beta waves

Alpha actiity ~ 200 μV

Hans Berger
1873 - 1941

http://www.slideshare.net/nikhilprerana/meg-final

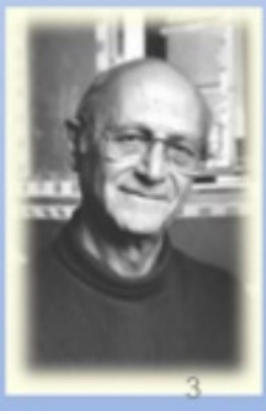
About 50 years later …

Brian-David Josephson

1968: first (noisy) measure of a magnetic brain signal *[Cohen, Science 68]*

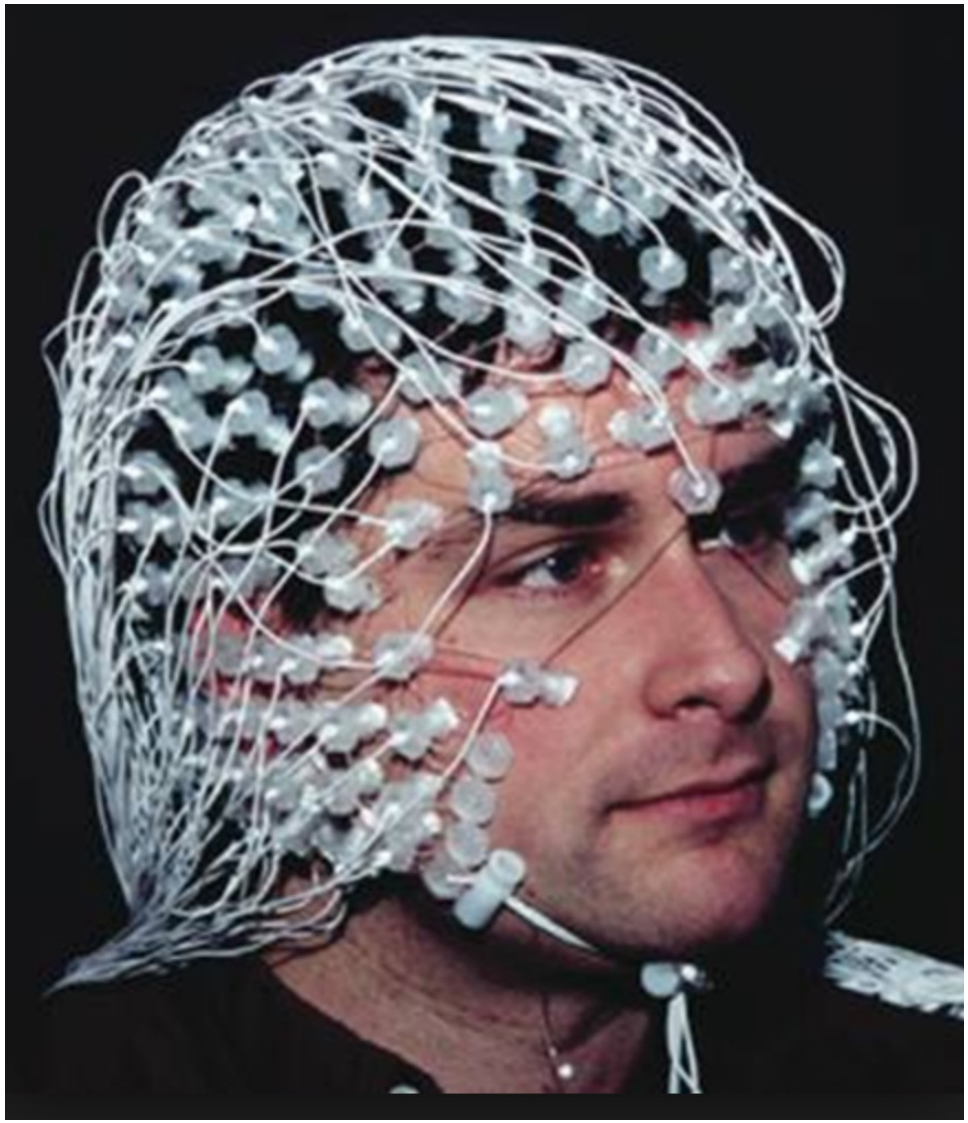
1970: James Zimmerman invents the
'*Superconducting quantum interference device*' (SQUID)

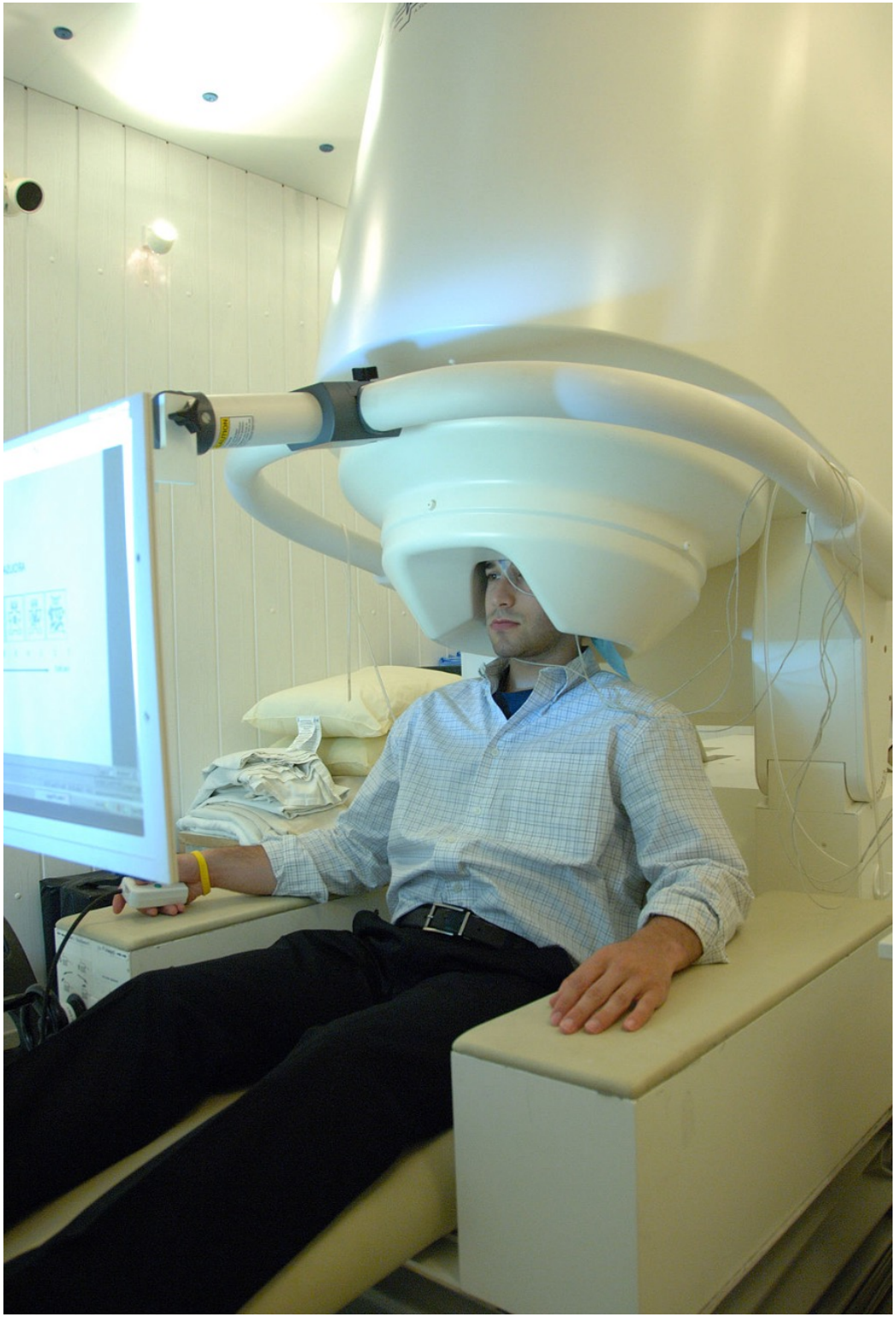
1972: first (1 sensor) MEG recording based on SQUID



David Cohen

http://www.slideshare.net/nikhilprerana/meg-final





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NeuroImage

Editor-in-Chief
Peter Bandettini

Special Issue
20 Years of fMRI: The Science and the Stories

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Peter Jezzard	Alan Koretsky	Fahmeed Hyder	Robert Savoy	David Norris	Steve Engel	Klaas Enno Stephan	John Baptiste Poline	Andrew Blamire	Kamil Ugurbil, Seiji Ogawa, Ravi Menon, Seong-Gi Kim	Mark Woolrich
David McGonigle	Tom Liu	Ken Kwong, Van Wedeen, Jack Belliveau, Bruce Rosen	Joe Mandeville	SPM	Dan Handwerker	Franz Schmitt, Mark Cohen	Eleanor Maguire	Christian Beckmann	Jim Haxby	Denis LeBihan
Jack and Amelie Belliveau	fMRI course cartoon from Robert Savoy	Alan Evans	Bruce Jenkins	Jia-Hong Gao	Ed Vul	Fa-Hsuan Lin	Tom Nichols	Multivariate Analysis Display from Niko Kriegeskorte	Peter van Gelderen	Rick Hoge
Jeff Duyn	David Feinberg	Hanzhang Lu	Mark Jenkenson	Randy McIntosh	Bruce Rosen	Afonso Silva	Bharat Biswal	Alard Roebroeck	Keith Thulborn	First MGH Functional Images
Rainer Goebel	Orientation Column fMRI data from Noam Harel	Steve Petersen, Joseph Dubis	Tom Talavage	Vince Clark	Gary Glover	Russ Poldrack	Seiji Ogawa	Eric Wong	Deb Hall	Krish Singh
Mark Lowe	Kamil Ugurbil	Uri Hasson	Susan Courtney	Elia Formisano	Peter Bandettini	Ed Bullmore	Network Connectivity Depictions from Steve Smith	Robert Weisskoff	Martin Lauritzen	Geoff Aguirre
FSL	Jurgen Reichenbach	James Hyde	Vascular Tree Depiction from Ravi Menon	Bruce Fischl	Scott Huettel	Bob Cox	Karla Miller	Ken Kwong	Nikos Logothetis	Keith Worsley
Ravi Menon	Robert Turner	Helmut Laufs	Kang Cheng	Xiaoping Hu	Andrzej Jesmanowicz	Rick Buxton	Olaf Sporns	AFNI	Larry Wald	Karl Friston
Stefan Posse	Brain Connectivity Display from Olaf Sporns	Peter van Zijl	John Ashburner	Rafi Malach	Jeff Binder	Heidi Johansen-Berg	Ziad Saad	Marcus Raichle, Avi Snyder	Niko Kriegeskorte, Marieke Mur	First fMRI results from Jack Belliveau (with gadolinium)
Geoff Boynton	Jurgen Hennig	Dave Rumelhart, Gary Glover, Brian Wandell	Seong-Gi Kim	Arno Villringer	Randy and Benjamin Buckner	First MCW Functional Image	Allen Song	Peter Bandettini, Eric Wong	Andreas Meyer-Lindenberg	Bruce Pike
Nikolaus Weiskopf	Steve Smith	Peter Fox	Gunnar Kreuger	Resting State Networks from Avi Snyder	Cathy Price	Rasmus Birn	Mark Haacke	Noam Harel	First U. Minn. Fuctional Images and Time Course	David Van Essen

Section	Paper Number	Paper Title	Author
Pre-fMRI	1	The science and the stories: fMRI over the past 20 years	Peter Bandettini
	2	My starting point: the discovery of an NMR method for measuring blood oxygenation using the transverse relaxation time of blood water	Keith Thulborn
	3	The coupling controversy	Peter Fox
	4	Early development of arterial spin labeling to measure regional brain blood flow by MRI	Alan Korestky
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	20	Ultrafast Inverse imaging techniques for fMRI	Fa-Hsuan Lin
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		simultaneously.	
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	96	The future of fMRI in clinical medicine	Ed Bullmore
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	99	The future of fMRI and genetics research	Andreas Meyer-Lindenberg
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	101	The future of the human connectome	David van Essen & Kamil Ugurbil
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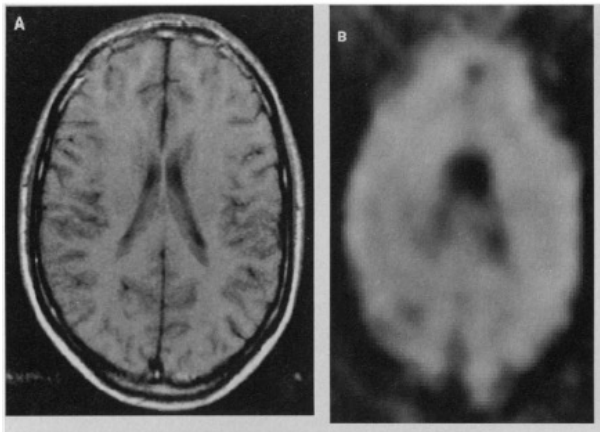
Functional Magnetic Resonance Imaging in Medicine and Physiology

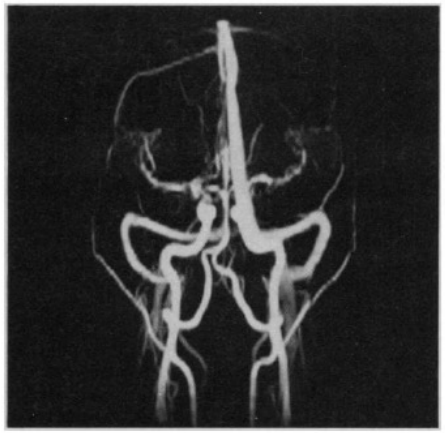
Chrit T. W. Moonen, Peter C. M. van Zijl, Joseph A. Frank, Denis Le Bihan, Edwin D. Becker

(1990) *Science*, 250, 53-61.

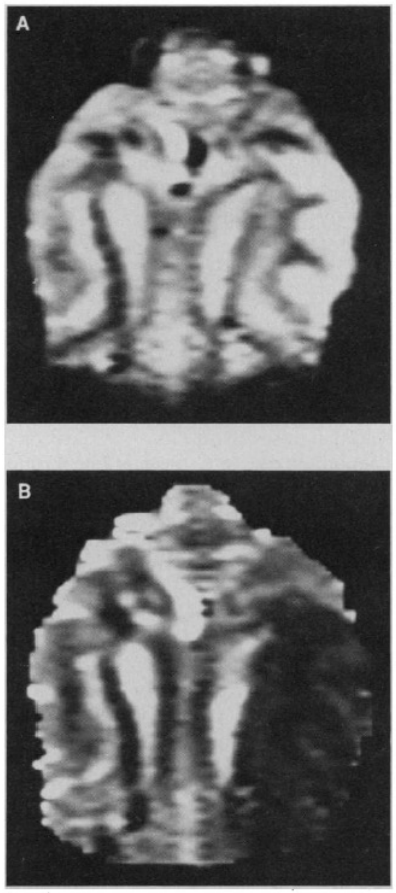
metabolic imaging (NAA)



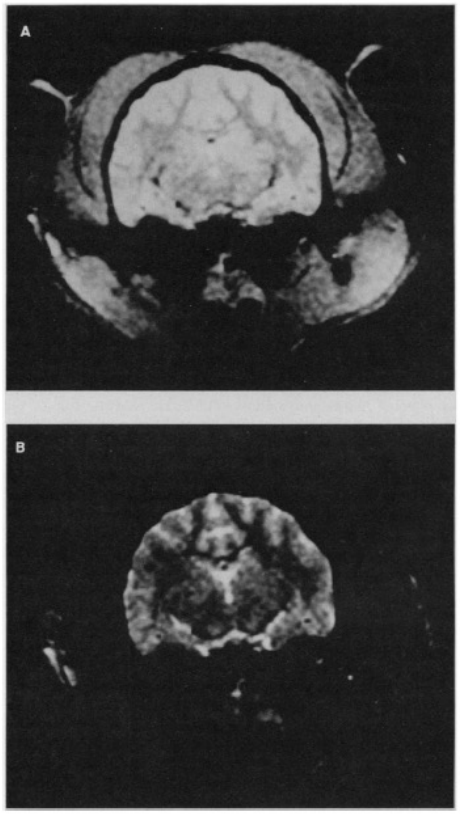
angiography

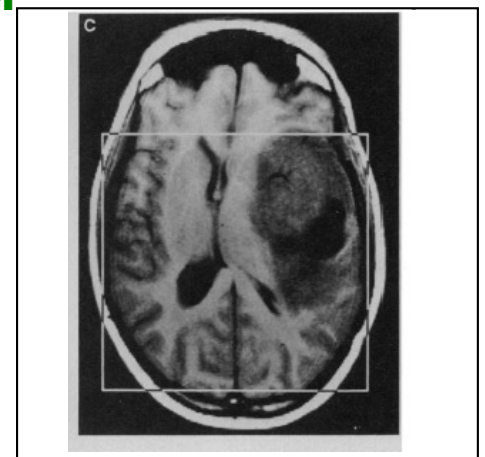


Diffusion

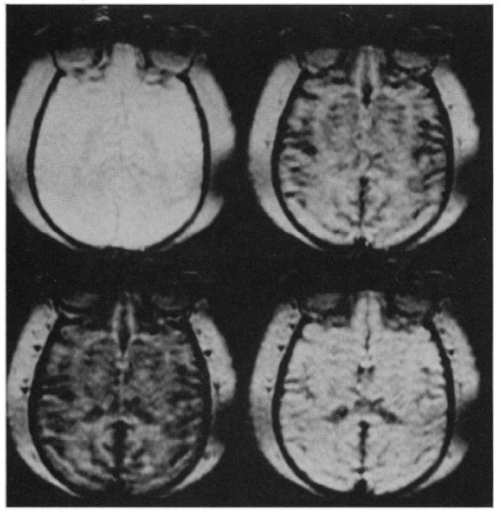


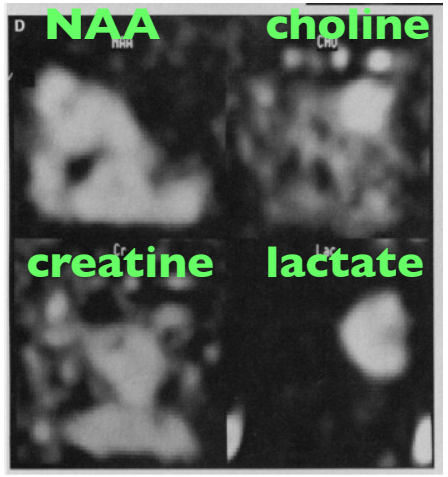
magnetization transfer





Gadolinium perfusion





How it all came together…

Five Key Factors For The Emergence of Functional MRI

1. **Magnetic properties of red blood cells**
2. **Activation related hemodynamic changes**
3. **Spatial scale of brain activation**
4. **Echo Planar Imaging**
5. **Prevalence of MRI scanners**

Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
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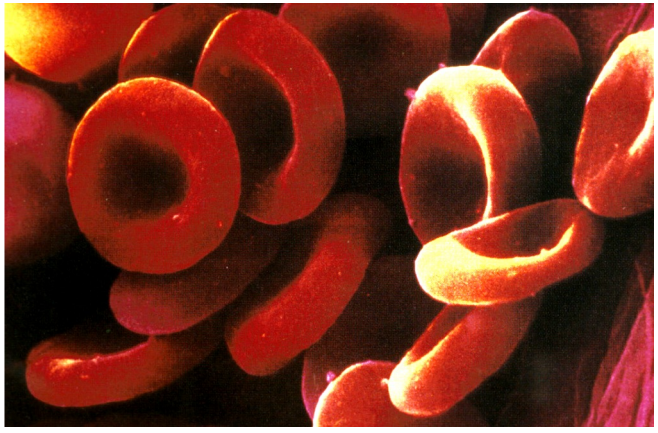
Magnetic Properties of Blood

L. Pauling, C. D. Coryell, *Proc.Natl.Acad. Sci. USA 22, 210-216*, **1936**.

K.R. Thulborn, J. C. Waterton, et al., *Biochim. Biophys. Acta. 714: 265-270*, **1982**.

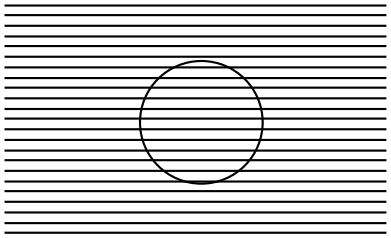
S. Ogawa, T. M. Lee, A. R. Kay, D. W. Tank, *Proc. Natl. Acad. Sci. USA 87, 9868-9872*, **1990**.

Turner, R., Lebihan, D., Moonen, C. T. W., Despres, D. & Frank, J. *Magnetic Resonance in Medicine,* 22, 159-166, **1991.**

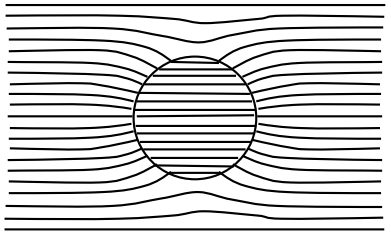


red blood cells

oxygenated



deoxygenated



BOLD contrast investigation started in 1936…or even 1845.

THE MAGNETIC PROPERTIES AND STRUCTURE OF HEMOGLOBIN, OXYHEMOGLOBIN AND CARBONMONOXYHEMOGLOBIN

BY LINUS PAULING AND CHARLES D. CORYELL

GATES CHEMICAL LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY

Communicated March 19, 1936

Over ninety years ago, on November 8, 1845, Michael Faraday investigated the magnetic properties of dried blood and made a note "Must try recent fluid blood." If he had determined the magnetic susceptibilities of arterial and venous blood, he would have found them to differ by a large amount (as much as twenty per cent for completely oxygenated and completely deoxygenated blood); this discovery without doubt would have excited much interest and would have influenced appreciably the course of research on blood and hemoglobin.[1]

Continuing our investigations of the magnetic properties and structure of hemoglobin and related substances,[2] we have found oxyhemoglobin and carbonmonoxyhemoglobin to contain no unpaired electrons, and ferrohemoglobin (hemoglobin itself) to contain four unpaired electrons per heme. The description of our experiments and the interpretation and discussion of the results are given below.

Biochimica et Biophysica Acta, 714 (1982) 265–270
Elsevier Biomedical Press

BBA 20122

OXYGENATION DEPENDENCE OF THE TRANSVERSE RELAXATION TIME OF WATER PROTONS IN WHOLE BLOOD AT HIGH FIELD

KEITH R. THULBORN, JOHN C. WATERTON *, PAUL M. MATTHEWS and GEORGE K. RADDA

Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU (U.K.)

(Received August 4th, 1981)

Key words: Oxygenation dependence; Transverse relaxation time; Water proton; High field NMR; (Whole blood)

At high and medium magnetic field, the transverse NMR relaxation rate (T_2^{-1}) of water protons in blood is determined predominantly by the oxygenation state of haemoglobin. T_2^{-1} depends quadratically on the field strength and on the proportion of haemoglobin that is deoxygenated. Deoxygenation increases the volume magnetic susceptibility within the erythrocytes and thus creates local field gradients around these cells.From volume susceptibility measurements and the dependence of T_2^{-1} on the pulse rate in the Carr-Purcell-Meiboom-Gill experiment, we show that the increase in T_2^{-1} with increasing blood deoxygenation arises from diffusion of water through these field gradients.

Oxygenation Changes T2

Biochimica et Biophysica Acta, 714 (1982) 265–270
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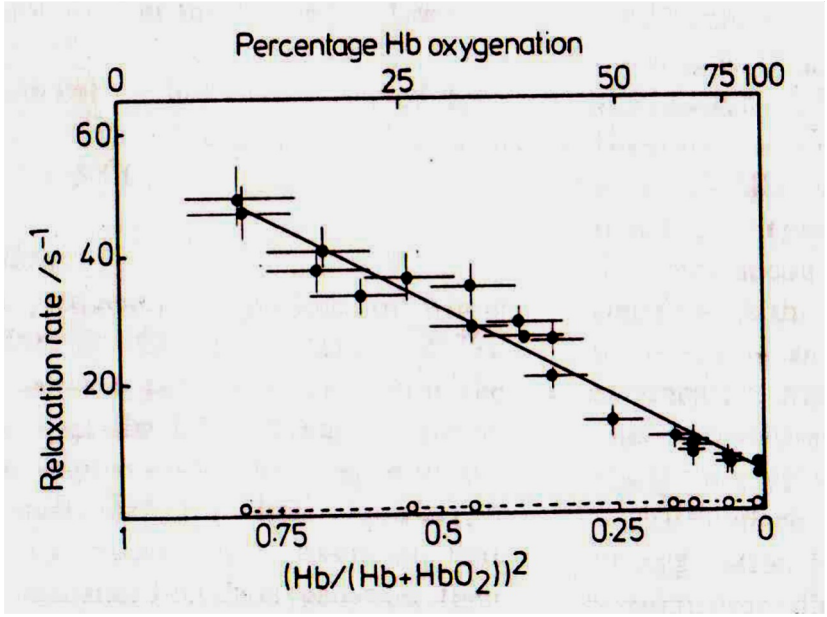
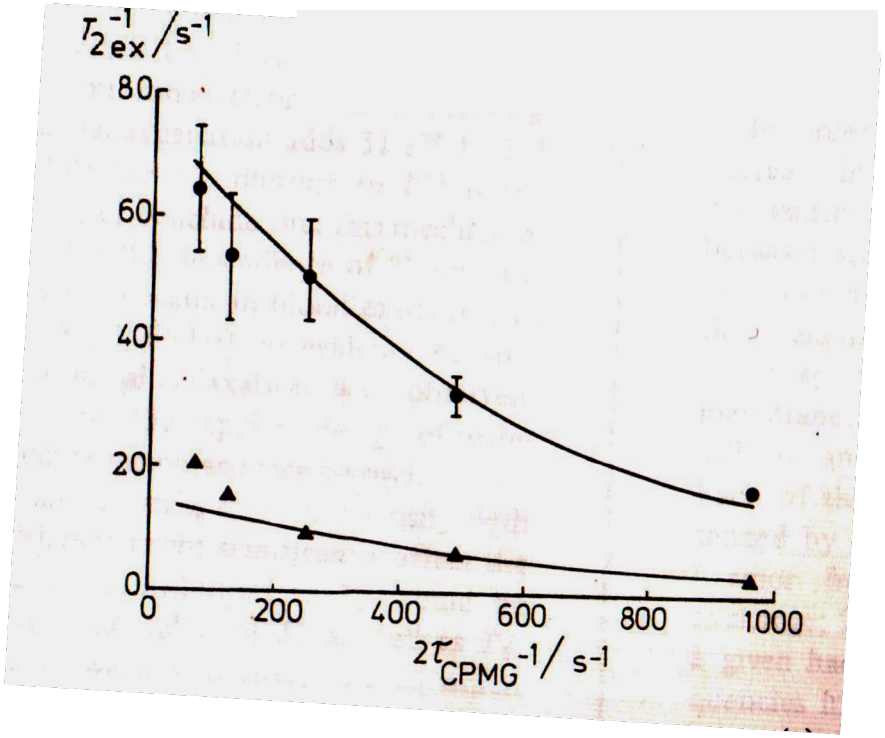
(Received August 4th, 1981)

R2 effect is due to bulk susceptibility and not dipole-dipole interaction

Blood R2 proportional to Oxygenation





...Six years later...

Oxygenation-Sensitive Contrast in Magnetic Resonance Image of Rodent Brain at High Magnetic Fields

SEIJI OGAWA, TSO-MING LEE, ASHA S. NAYAK,* AND PAUL GLYNN

AT&T Bell Laboratories, Murray Hill, New Jersey 07974

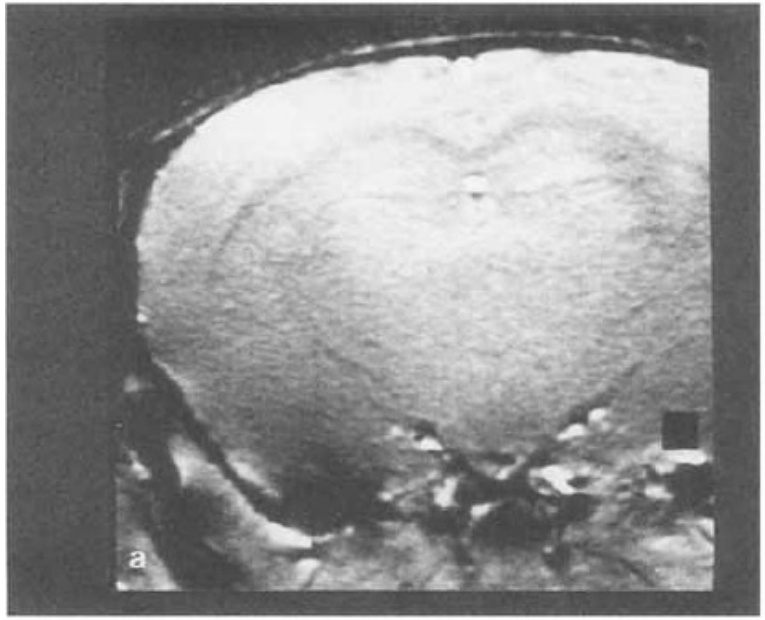
Received November 30, 1988; accepted June 20, 1989

At high magnetic fields (7 and 8.4 T), water proton magnetic resonance images of brains of live mice and rats under pentobarbital anesthetization have been measured by a gradient echo pulse sequence with a spatial resolution of 65 × 65-μm pixel size and 700-μm slice thickness. The contrast in these images depicts anatomical details of the brain by numerous dark lines of various sizes. These lines are absent in the image taken by the usual spin echo sequence. They represent the blood vessels in the image slice and appear when the deoxyhemoglobin content in the red cells increases. This contrast is most pronounced in an anoxy brain but not present in a brain with diamagnetic oxy or carbon monoxide hemoglobin. The local field induced by the magnetic susceptibility change in the blood due to the paramagnetic deoxyhemoglobin causes the intra voxel dephasing of the water signals of the blood and the surrounding tissue. This oxygenation-dependent contrast is appreciable in high field images with high spatial resolution.

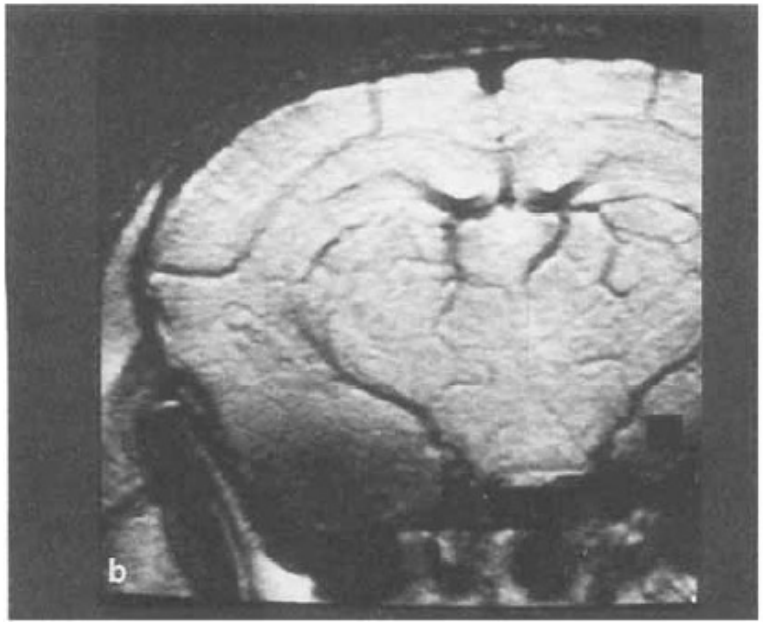
in vivo

in vitro

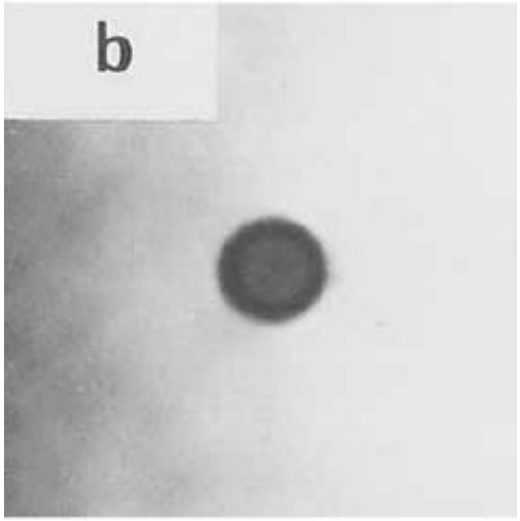
100% O_2



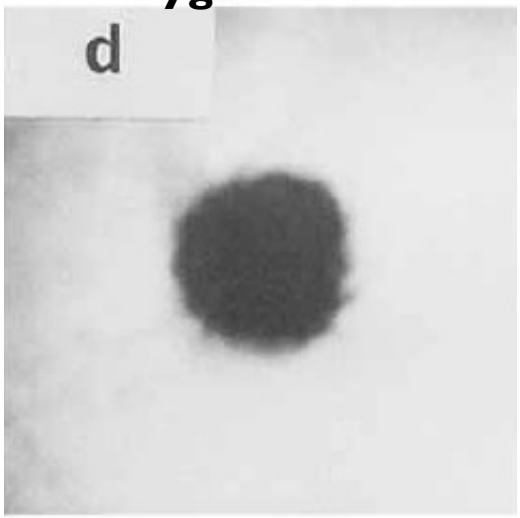
20% O_2



100% oxygenated blood

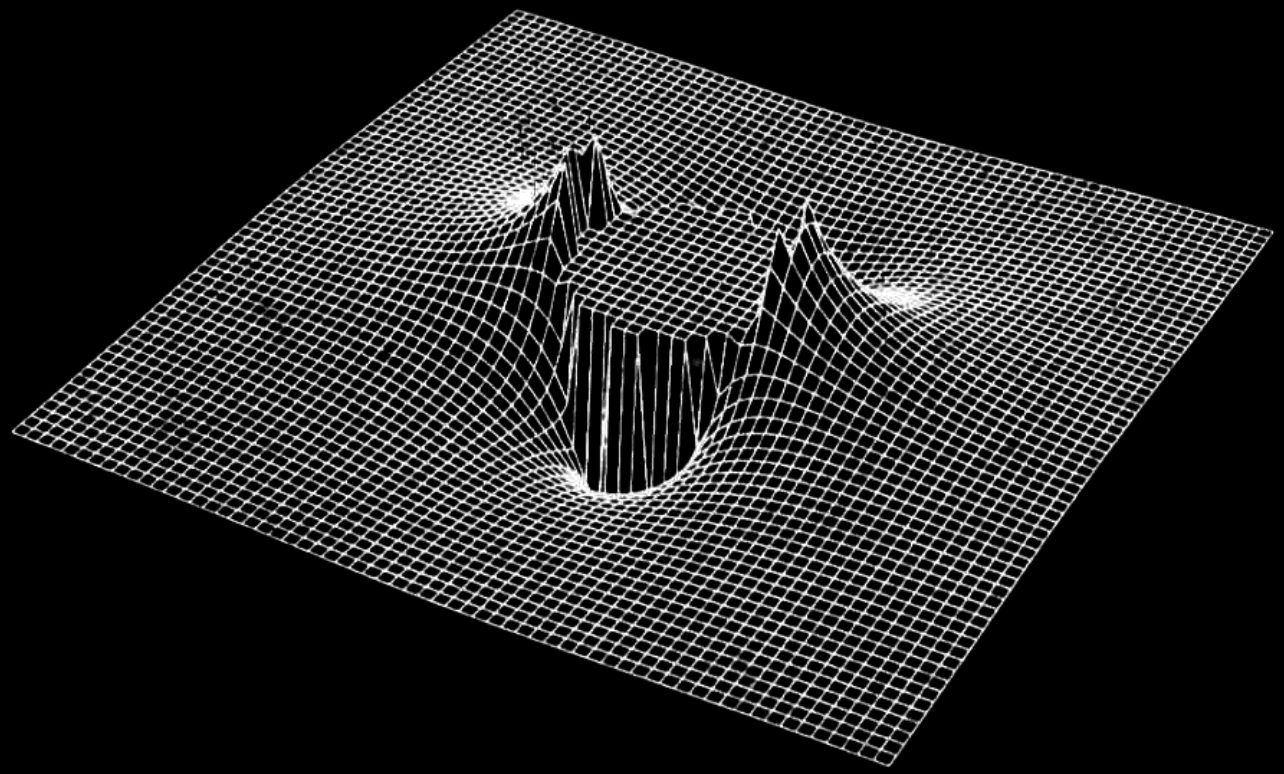


0% oxygenated blood



S. Ogawa, T.-M. Lee, A. S. Nayak, P. Glynn, Magn. Reson. Med, 14, 68-78 (1990)

Susceptibility-Induced Field Distortion in the Vicinity of a Microvessel $\perp$ to B_O.



MAGNETIC RESONANCE IN MEDICINE 22, 159–166 (1991)

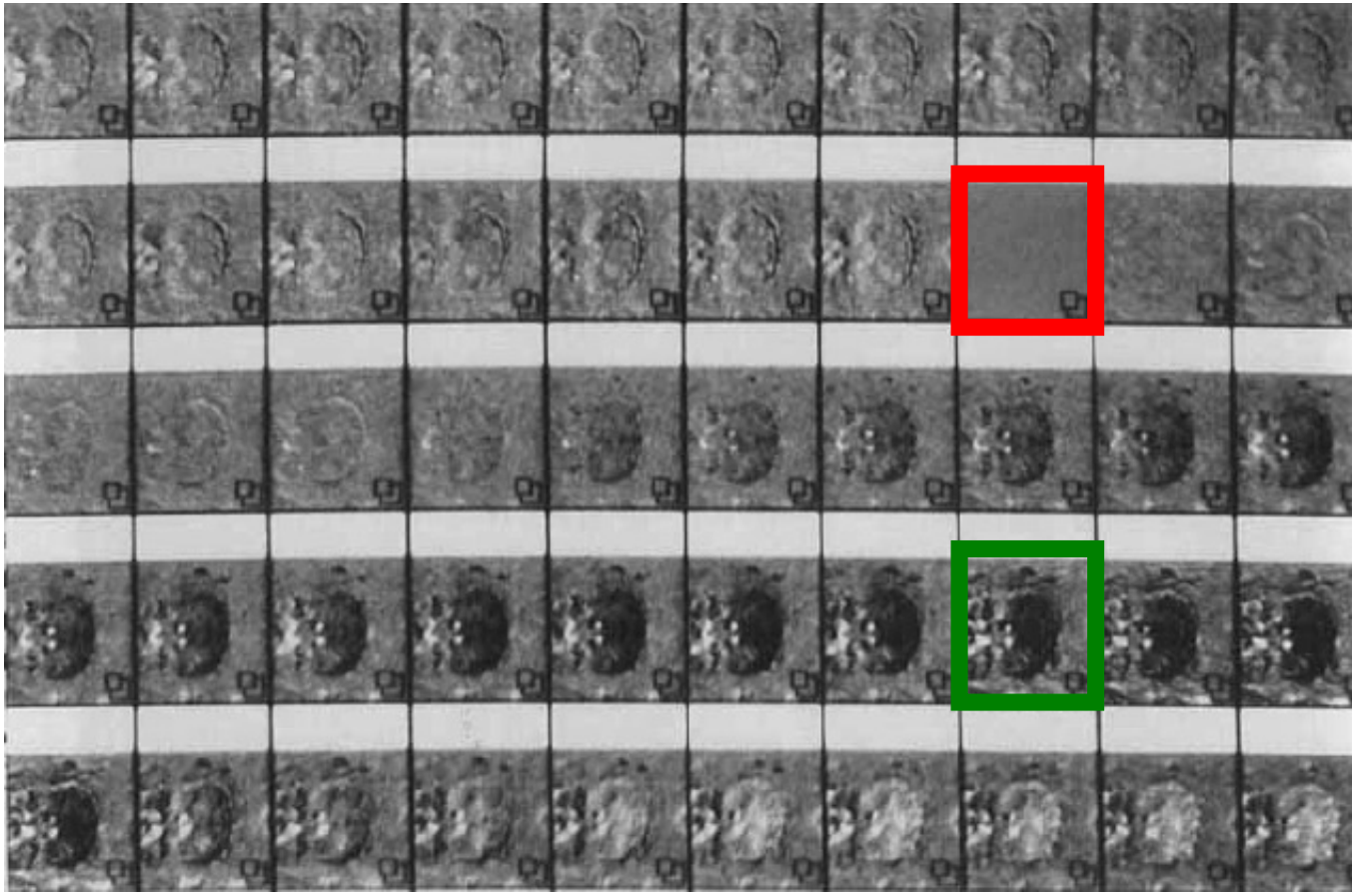
Echo-Planar Time Course MRI of Cat Brain Oxygenation Changes

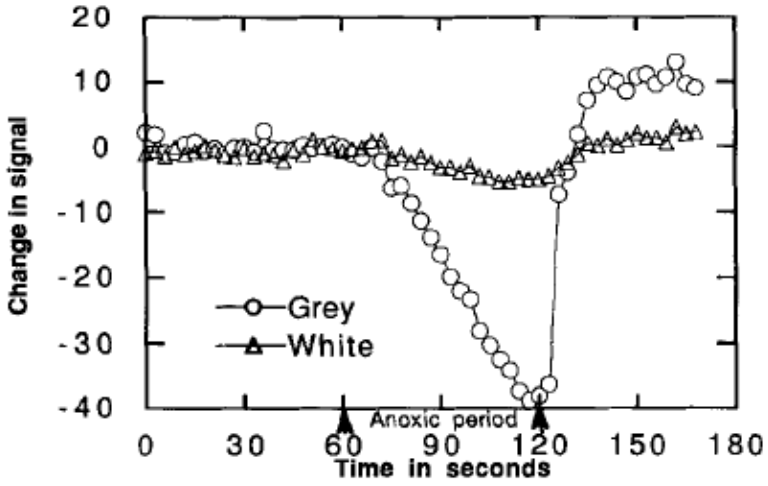
ROBERT TURNER,*† DENIS LE BIHAN,‡ CHRIT T. W. MOONEN,§
DARYL DESPRES,§ AND JOSEPH FRANK‡

* *Laboratory of Cardiac Energetics,* ‡ *Diagnostic Radiology Department, and* § *In Vivo NMR Research Center, National Institutes of Health, Bethesda, Maryland 20892*

Received June 25, 1991; revised August 7, 1991

When deoxygenated, blood behaves as an effective susceptibility contrast agent. Changes in brain oxygenation can be monitored using gradient-echo echo-planar imaging. With this technique, difference images also demonstrate that blood oxygenation is increased during periods of recovery from respiratory challenge.





R. Turner, D. LeBihan, C.T.W. Moonen, D. Despres, J. Frank, Magn. Reson. Med, 22, 159-166 (1991)

Ogawa predicted fMRI but got the sign wrong…

"...we expect this oxygenation-sensitive contrast could be used to monitor regional oxygen usages in the brain. When some region in a brain is much more active than other regions, the active region could show darker lines in the image because of the increased level of deoxyhemoglobin resulting from higher oxygen consumption."

"Therefore, in addition to the anatomy of the brain, one aspect of its physiology can be studied by the MRI of water"

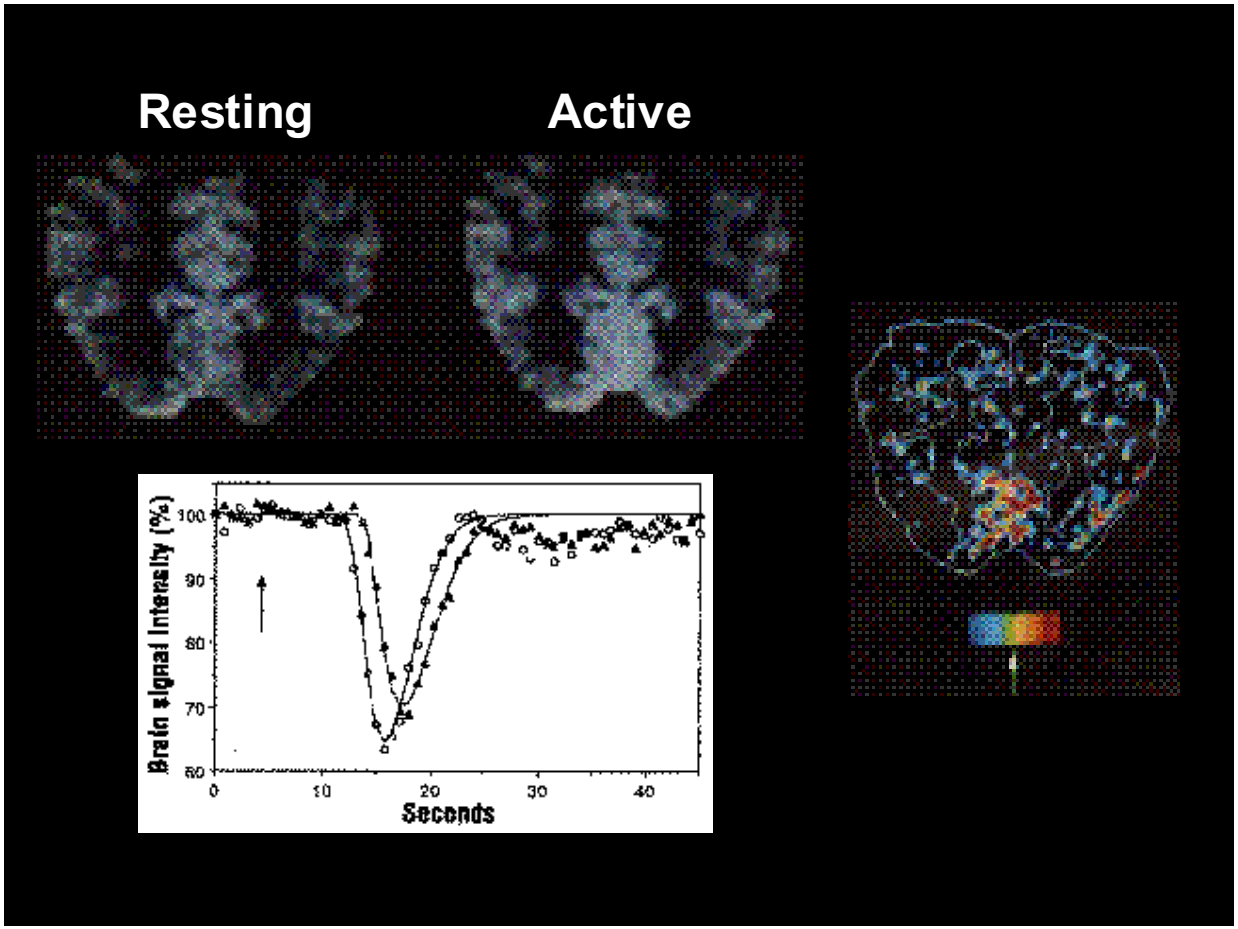
Oxygenation-Sensitive Contrast in Magnetic Resonance Image of Rodent Brain at High Magnetic Fields, Seiji Ogawa, Tso-Ming Lee, Asha S. Nayak, and Paul Glynn.**Magnetic Resonance in Medicine 14, 68-78 (1990).**

Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

The First Functional MRI Results (MGH)

Susceptibility Contrast agent bolus injection and time series collection of T2 - weighted images



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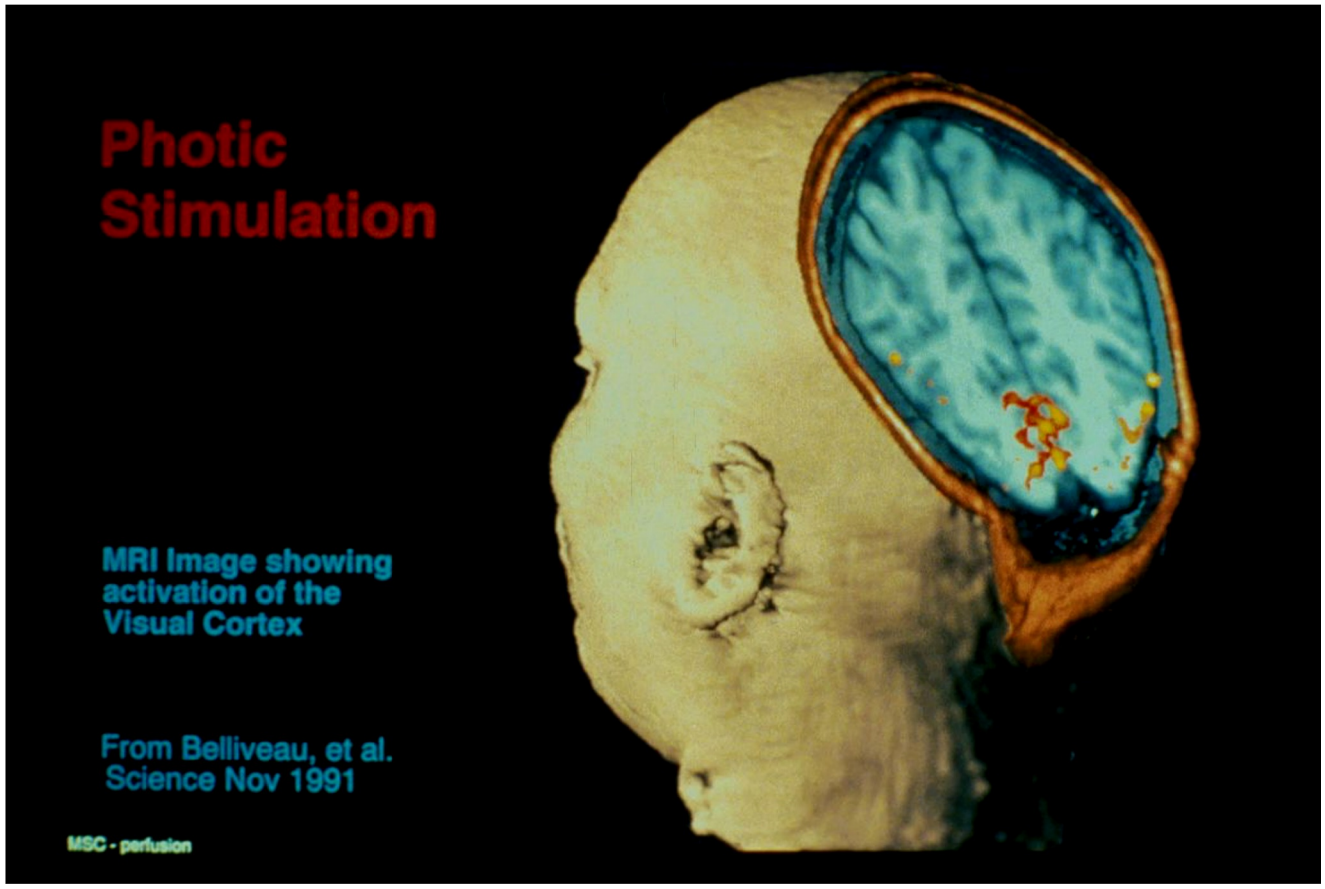


The MGH Gang

Jack Belliveau, Explorer of the Brain Using M.R.I., Dies at 55

By **BENEDICT CAREY** MARCH 9, 2014

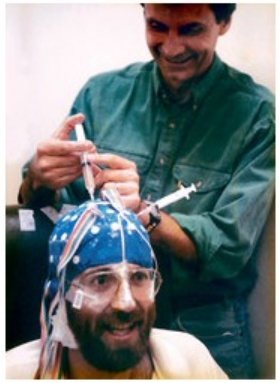
Jack Belliveau

Jack Belliveau, a Harvard scientist whose quest to capture the quicksilver flare of thought inside a living brain led to the first magnetic resonance image of human brain function, died on Feb. 14 in San Mateo, Calif. He was 55.

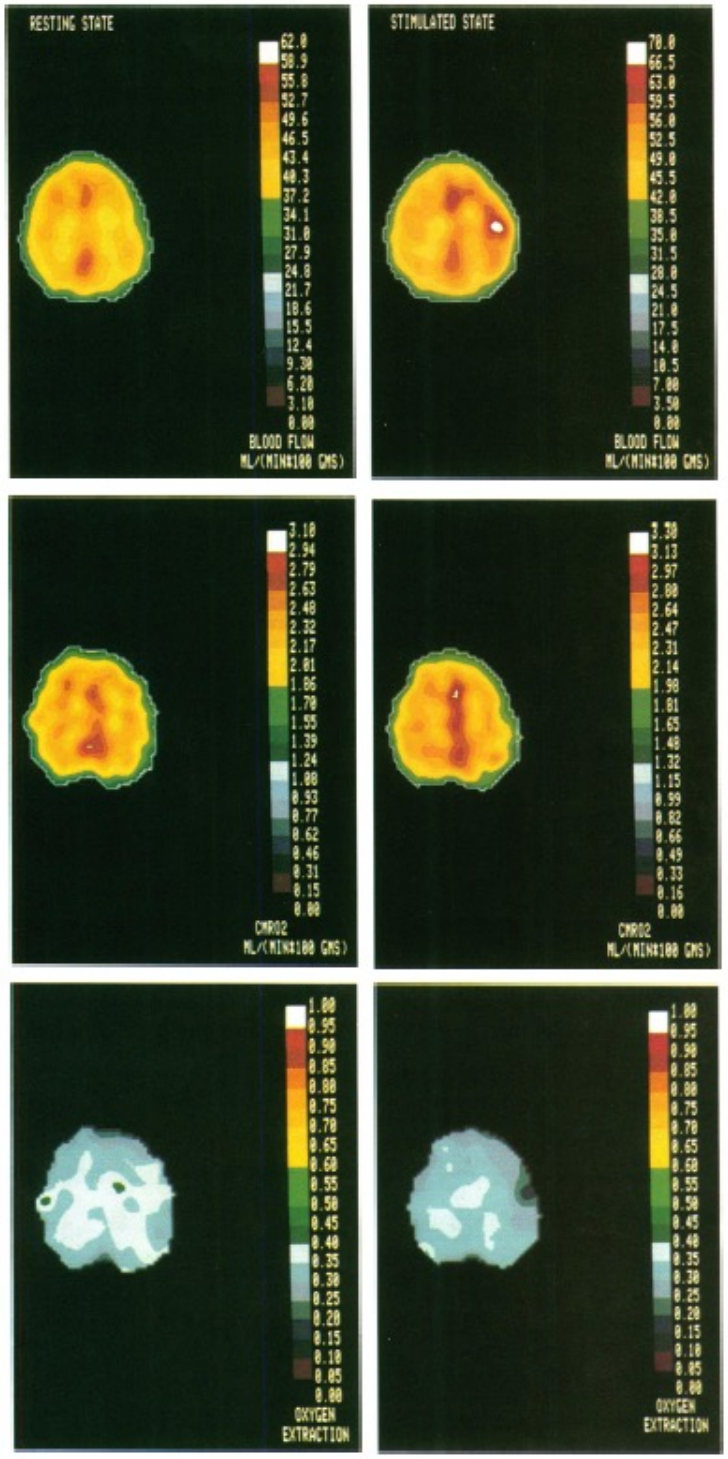
The cause was complications of a gastrointestinal disorder, said his wife, Brigitte Poncelet-Belliveau, a researcher who worked with him at the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital. He lived in Boston. His wife said he died suddenly while visiting an uncle at his childhood home, which he owned.

Dr. Belliveau was a 30-year-old graduate student at the Martinos Center when he hatched a scheme to "see" the neural trace of brain activity. Doctors had for decades been taking X-rays and other images of the brain to look for tumors and other lesions and to assess damage from brain injuries. Researchers had also mapped blood flow using positron emission tomography scans, but that required making and handling radioactive trace chemicals, whose signature vanished within minutes. Very few research centers had the technical knowledge or the machinery to pull it off.

Dr. Belliveau tried a different approach. He had developed a technique to track blood flow, called dynamic susceptibility contrast, using an M.R.I. scanner that took split-second images, faster than was usual at the time. This would become a standard technique for assessing blood perfusion in stroke patients and others, but Dr. Belliveau thought he would try it to spy on a normal brain in the act of thinking or perceiving.



Jack Belliveau, seated for an experimental EEG, with his colleague Gregory Simpson. Harvard Medical School



Proc. Natl. Acad. Sci. USA
Vol. 83, pp. 1140–1144, February 1986
Neurobiology

Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects

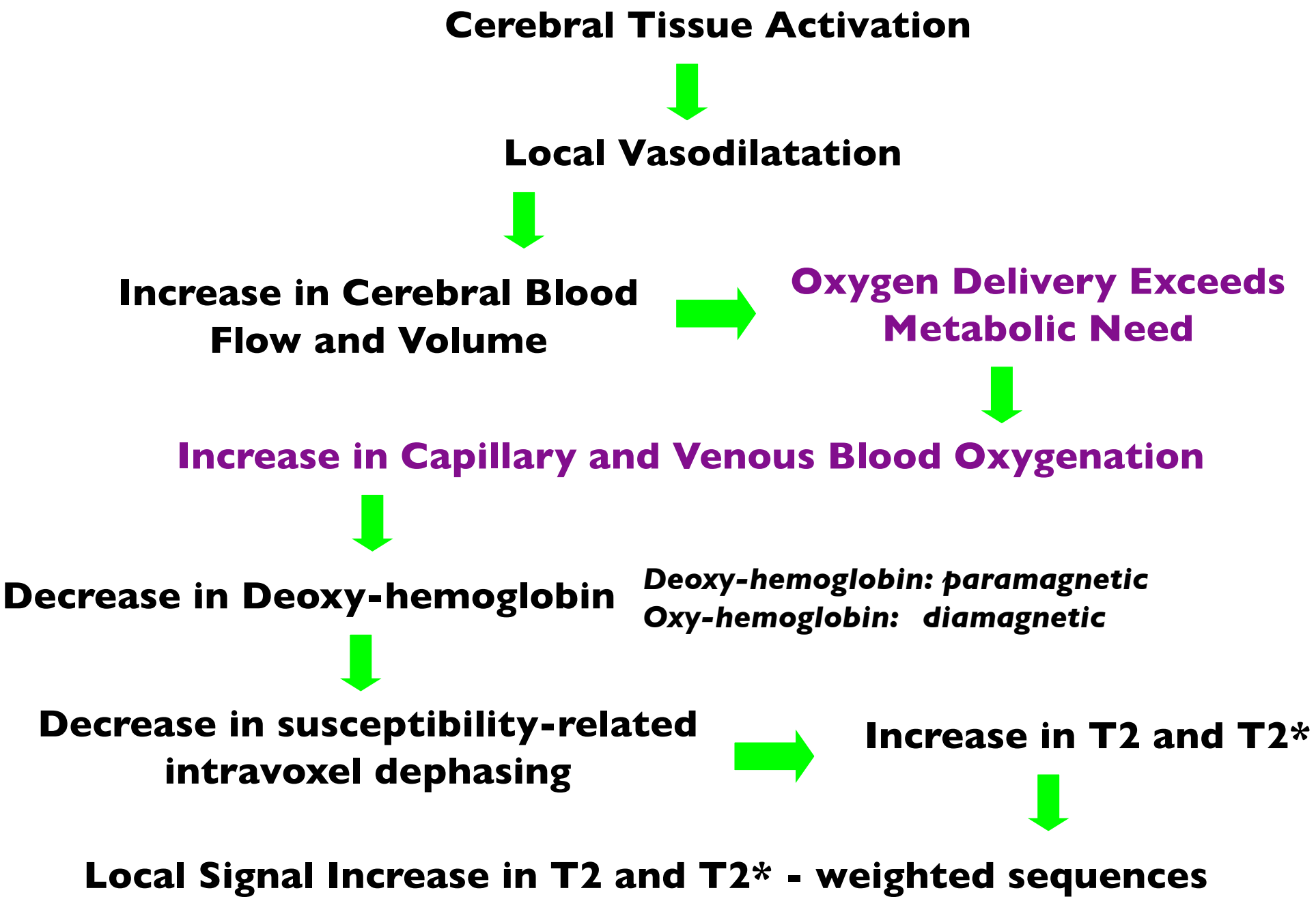
(positron emission tomography)

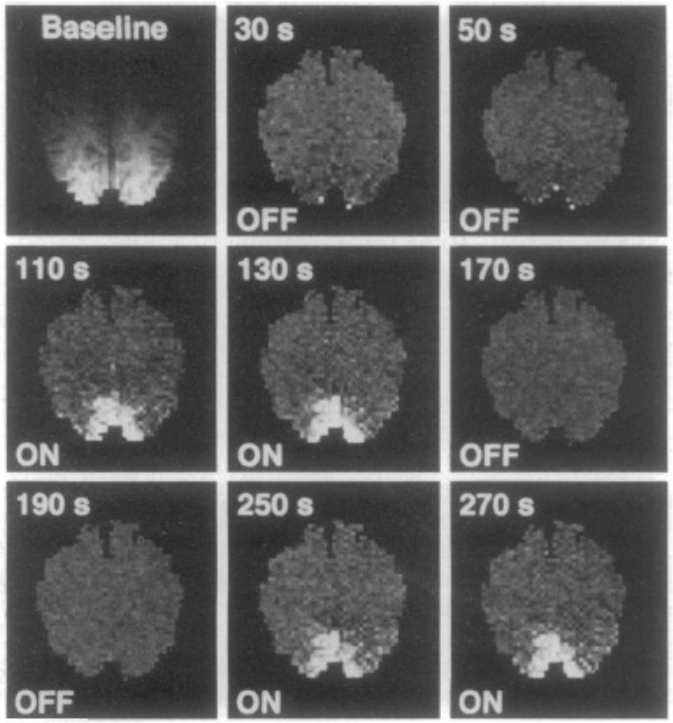
PETER T. FOX*†‡ AND MARCUS E. RAICHLE*†

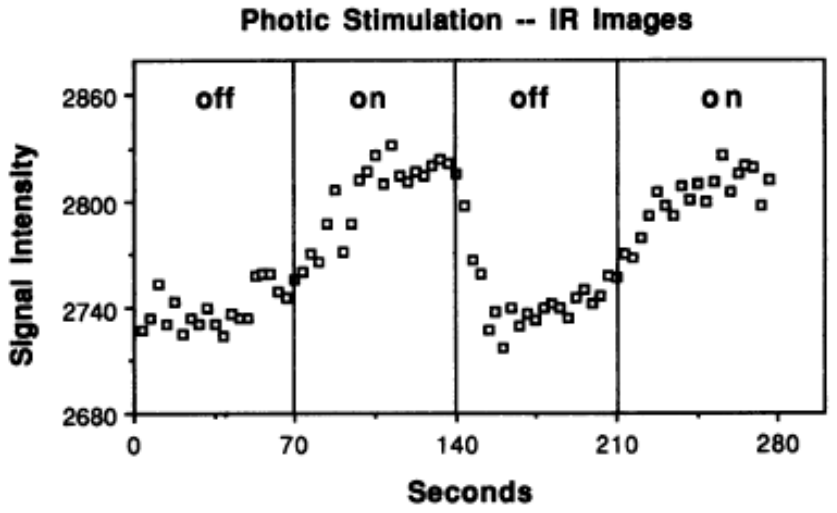
*Department of Neurology and Neurological Surgery (Neurology), †Department of Radiology (Radiation Sciences), and The McDonnell Center for Studies of Higher Brain Function, Washington University School of Medicine, St. Louis, MO 63110

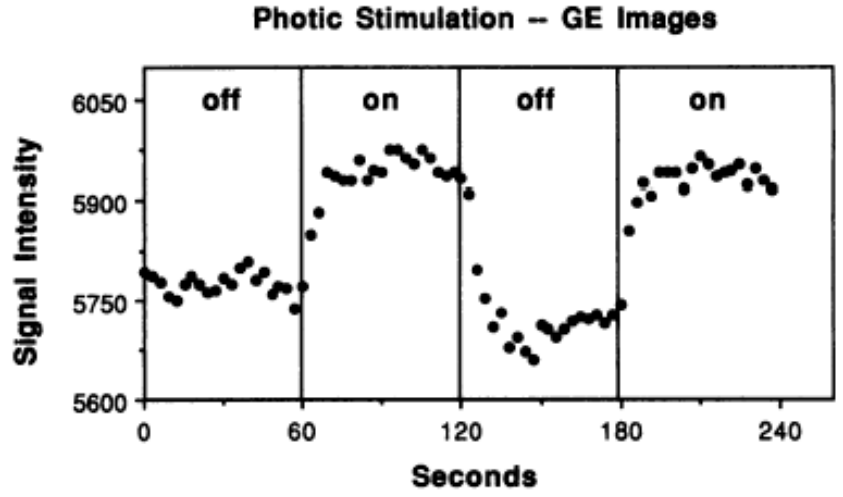
Communicated by Oliver H. Lowry, October 7, 1985

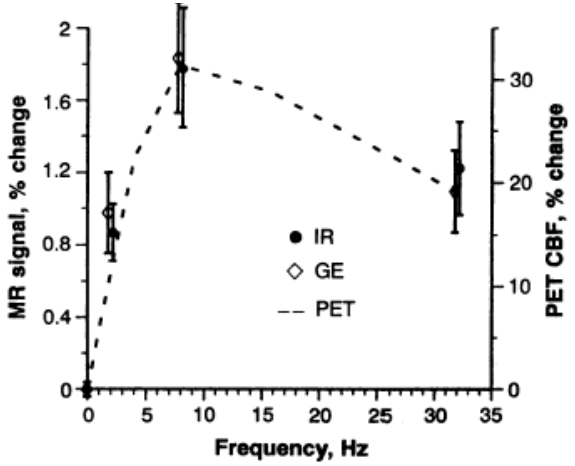
FIG. 1. Physiological uncoupling of brain blood flow and metabolism. (*Left*) Resting-state measurements. (*Right*) Stimulated-state measurements (unilateral vibrotactile stimulation of the fingers). All images are from a single subject's scanning session and pass through the same brain plane. Color scales are linear with the maxima set at a fixed multiple (1.6) of the global average, to facilitate visual comparisons (16). During specific somatosensory stimulation a marked focal increase in CBF (29% of mean, nine subjects, three trials per subject) was produced in the contralateral sensorimotor cortex. The observed increase in the $CMRO_2$ was much smaller (5% of mean, nine subjects, three trials per subject) and failed to attain significance. This physiological uncoupling of CBF and $CMRO_2$ flow produced a highly significant decrease in the local OEF (−19% of mean), indicating that tissue Po_2 (and probably pH) rose during stimulation. Note that, although the data were analyzed as contralateral/ipsilateral ratios (see text and Tables 1–4), the disparity between blood flow and metabolism was evident from the raw data and was not dependent on a particular strategy of analysis.


Cerebral Tissue Activation
Local Vasodilatation
Increase in Cerebral Blood Flow and Volume
Oxygen Delivery Exceeds Metabolic Need
Increase in Capillary and Venous Blood Oxygenation
Decrease in Deoxy-hemoglobin
Deoxy-hemoglobin: paramagnetic
Oxy-hemoglobin: diamagnetic
Decrease in susceptibility-related intravoxel dephasing
Increase in T2 and T2*
Local Signal Increase in T2 and T2* - weighted sequences









K. K. Kwong, et al, (1992) "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation." **Proc. Natl. Acad. Sci. USA. 89, 5675-5679.**

photo sti. 5 in GP

~~GRE~~
IR

GE 350
70 sec stim
disdaq=2 | 30 pre | 40 post

2.5

IR
disdaq =2 | 3.0 TR
40 pre 40 post

TI = 1.05 s.

SQ
80
20 | 30 | 20

90 sec
80
40 | 40

20 20 20

10 cm. slice cardiac

removing spikes
irstim.pre 2 3 5-8 13 14 16 18 19 25-29 (16 together)
irstim.pos 34-38 40-47 49-65 67-80 (44 together)
Avg them (with seqavg x51v)
Set mirstim.avg (save them)

10 cm. slice cardiac
TR=2.5 S TE=40
GE TA = 109
RA = 350
7106

MAY 9, 91

Michelle

30 TR 40 on

GEstim.dat
gestim.pre 3-30 (28)
gestim.poo 33-70 (38)
30 3.0
2.3
~~gest~~ gepre.avg
gepos.avg
7106
gestim.avg
gstim.sub 28
7106

IR RA 370 TA 102

TR=3S TI = 1100 ms TE = 42

~~40~~ → 40
30 50

IR Image 66
jump up.

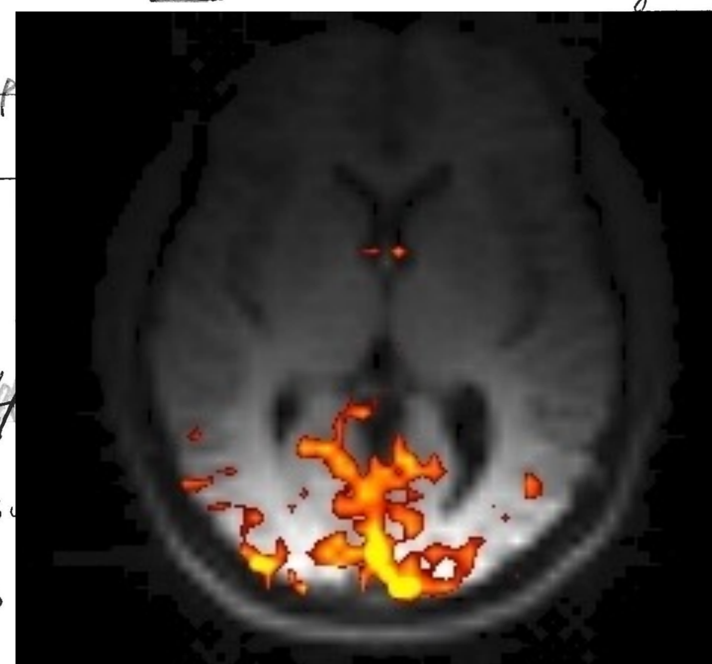
~~irstim.p~~
irstim

irstim.

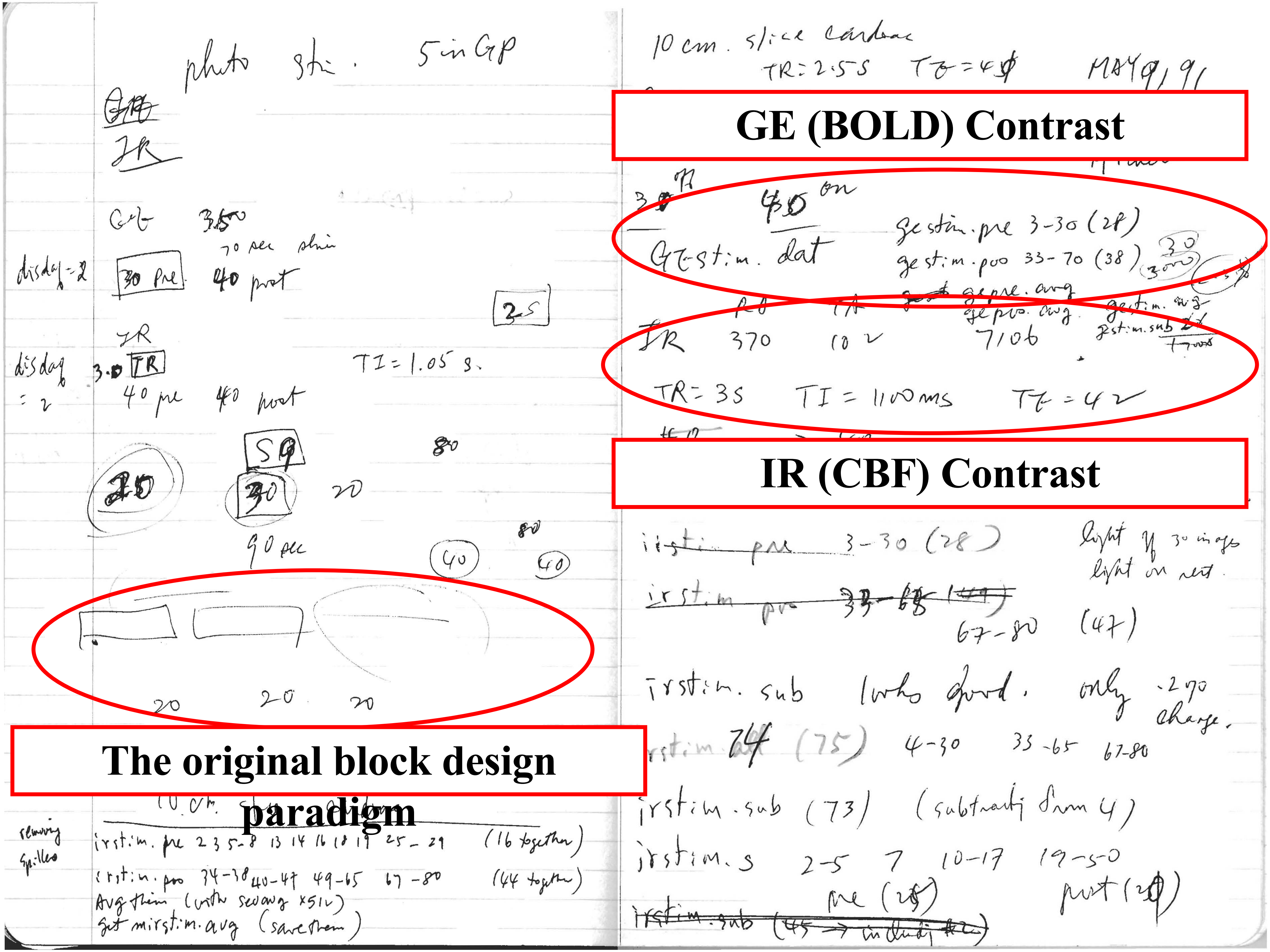
irstim. 74

irstim.s

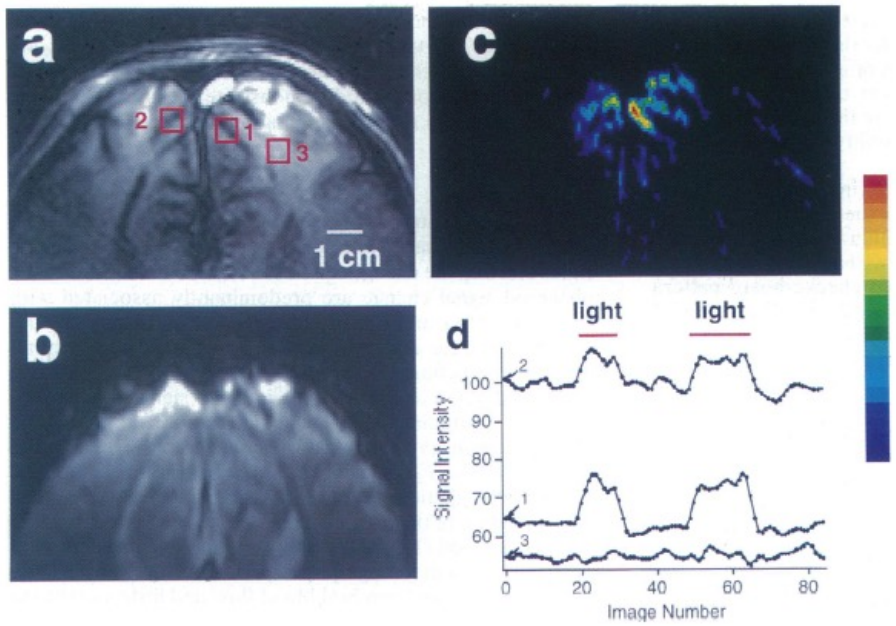
irstim.s



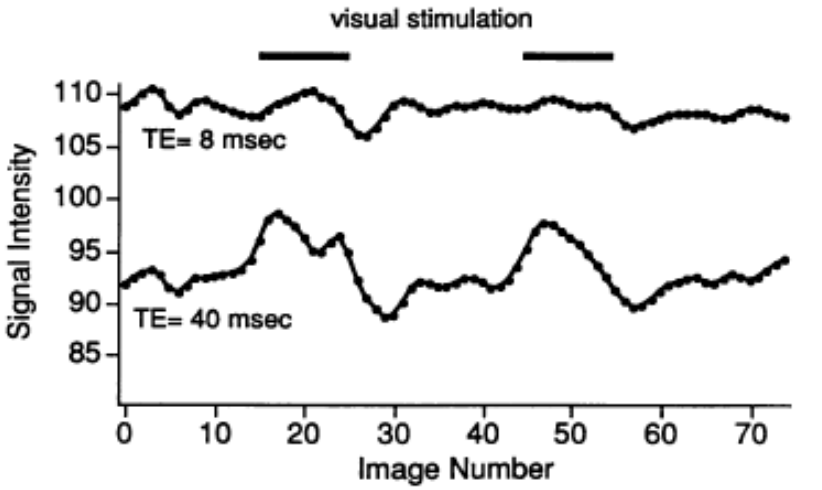
~~irstim.sub~~ (~~45 → including #2~~)

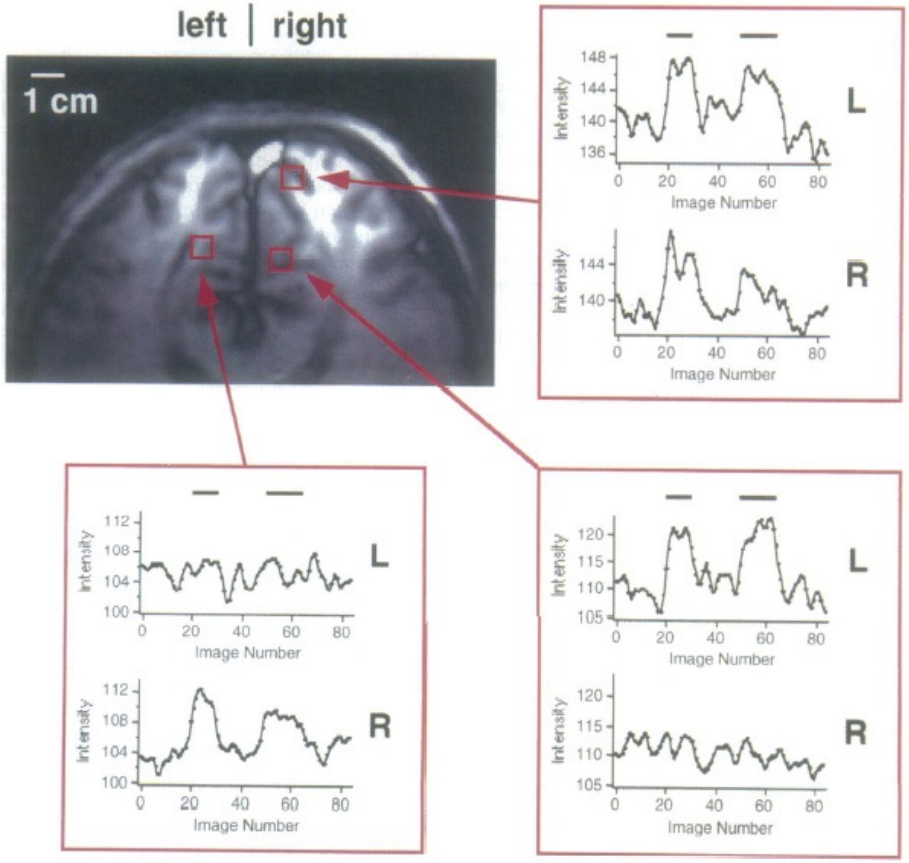

GE (BOLD) Contrast
IR (CBF) Contrast
The original block design paradigm

Multi-shot results at 4T, U. Minnesota.

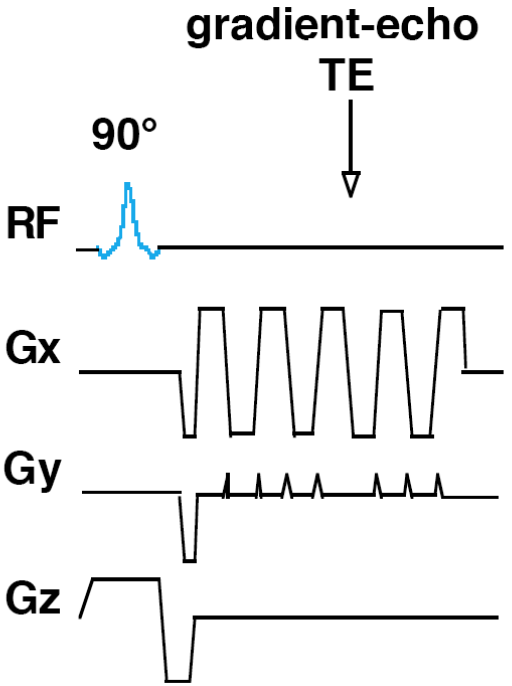


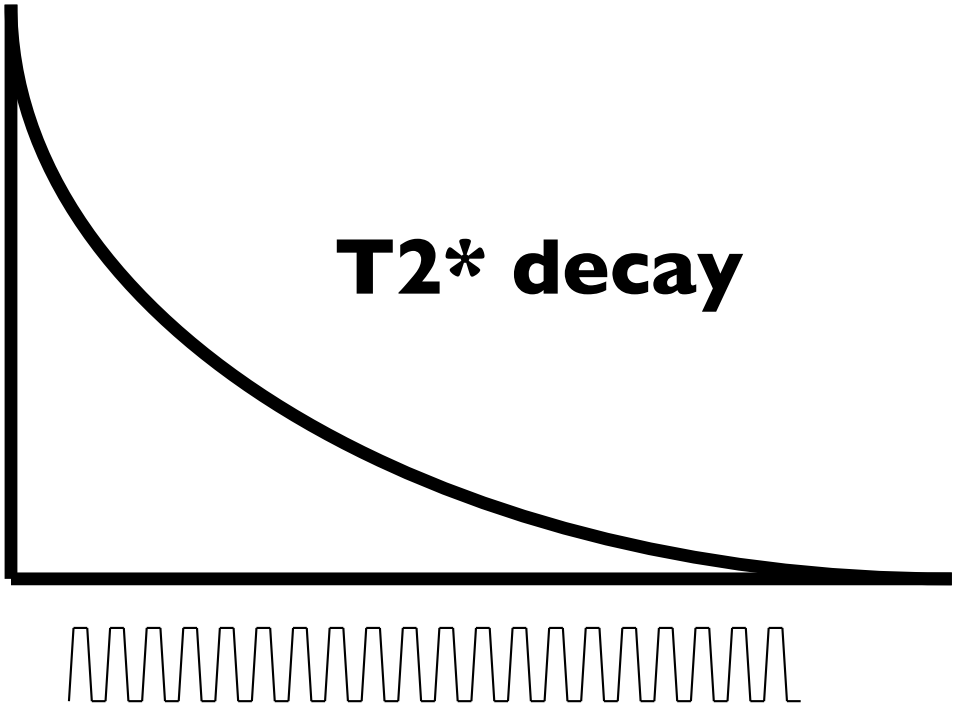
S. Ogawa, et al., (1992) "Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging." Proc. Natl. Acad. Sci. USA. 89, 5951-5955.





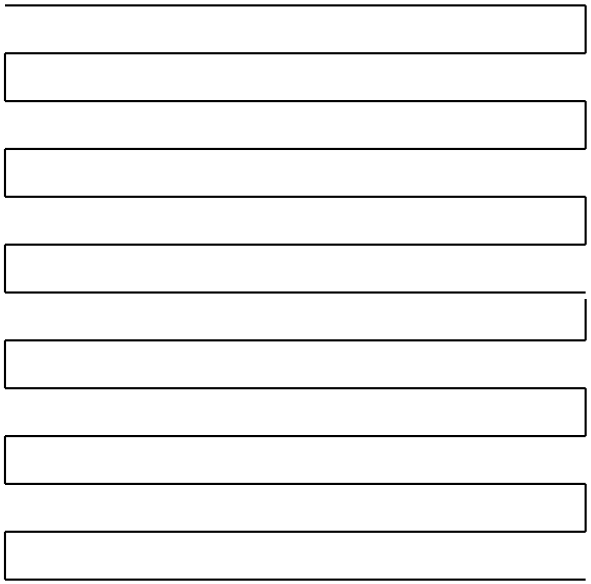
Single Shot Echo Planar Imaging (EPI)





EPI Readout Window

≈ 20 to 40 ms



First Fast Imaging Approaches

1. **MGH: ANMR retrofitted resonant gradient system with EPI**

2. **Minnesota: Standard gradients with Multi-shot with navigator echoes**

3. **MCW: local low-inductance gradient coil with EPI**

What preceded the results from the Medical College of Wisconsin…

MAGNETIC RESONANCE IN MEDICINE 21, 39–48 (1991)

Coil Optimization for MRI by Conjugate Gradient Descent

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Biophysics Section, Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226

Received April 30, 1990; revised June 29, 1990

Local head gradient coils: Window(s) of opportunity

Eric C. Wong

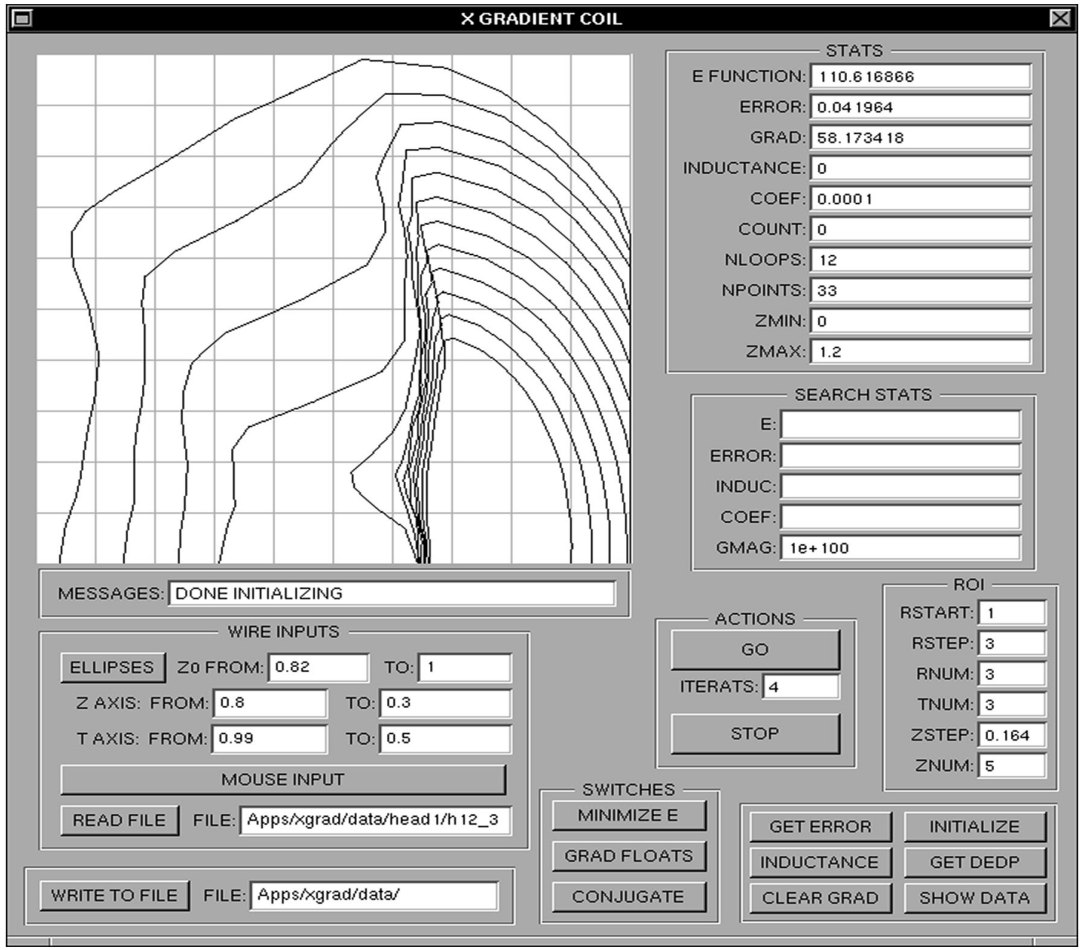
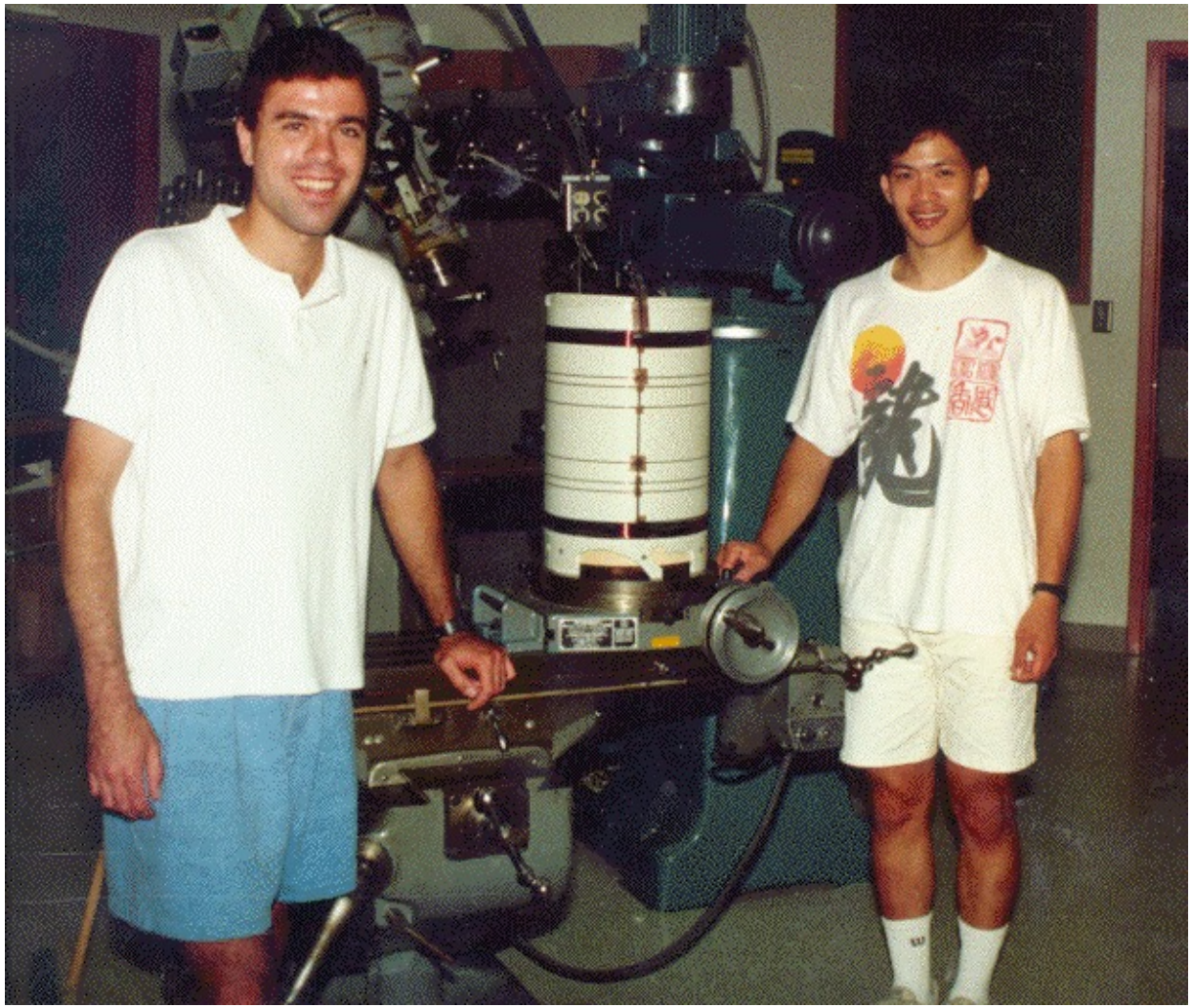


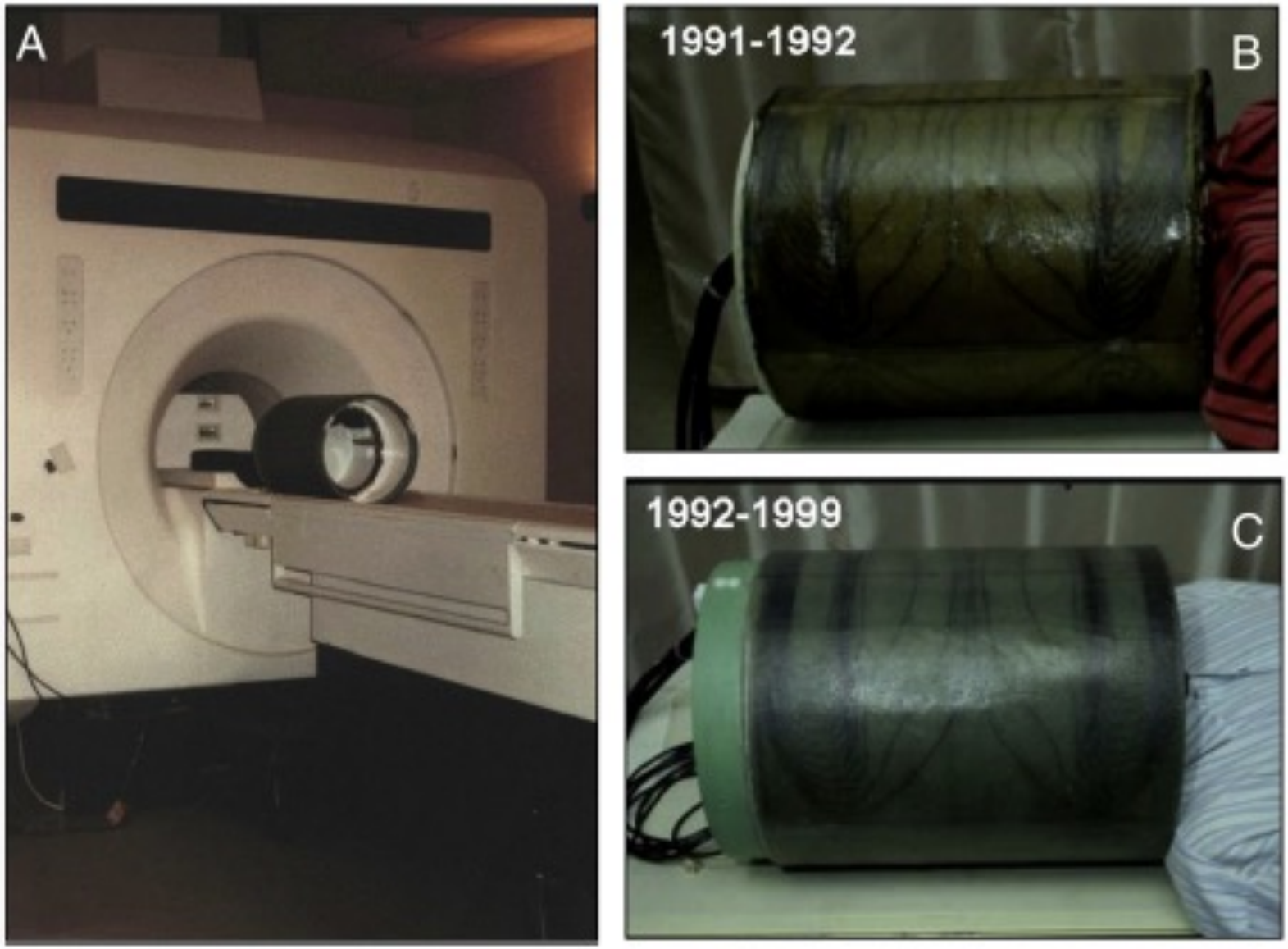
Fig. 1 GUI for gradient descent gradient coil design tool. The design shown is one octant of the X gradient coil designed and built in August 1991. The program was written in Objective C and ran on a NeXT Cube computer.

NeuroImage, Volume 62, Issue 2, 2012, 660 - 664

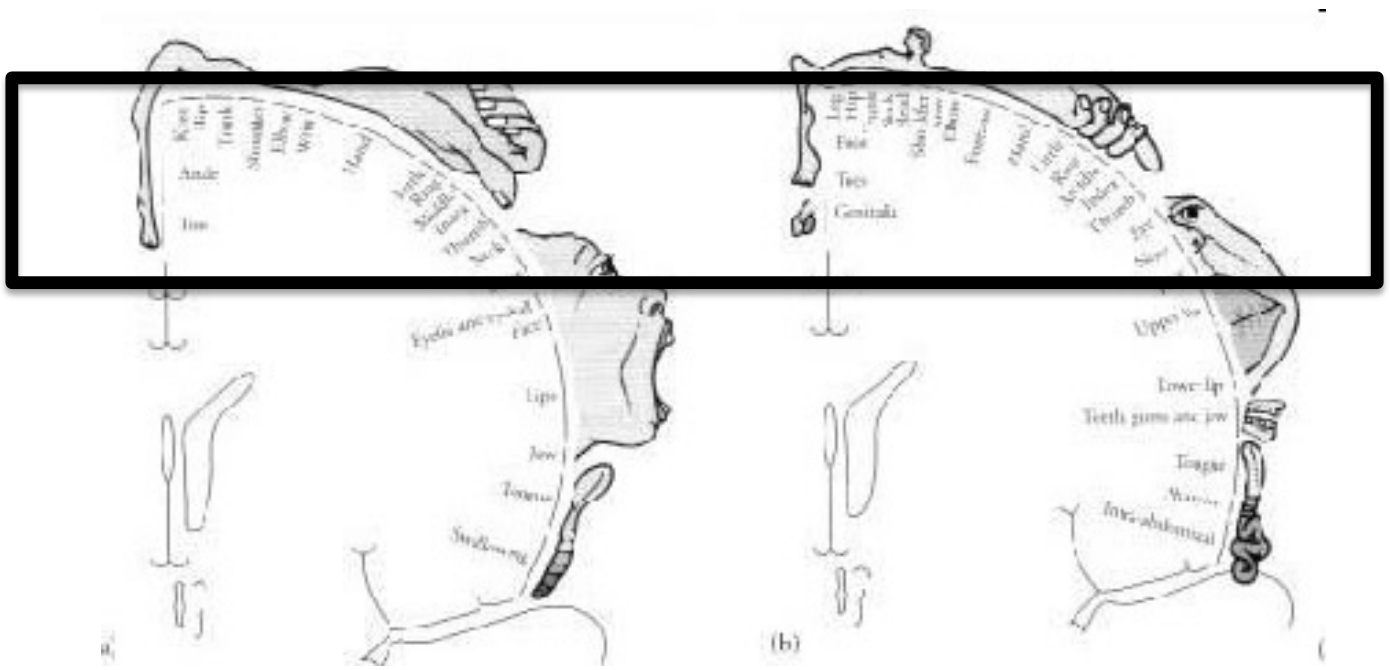
http://dx.doi.org/10.1016/j.neuroimage.2012.01.025



August, 1991


A
1991-1992
B
1992-1999
C

Initially could only do one slice…



2.5 cm !

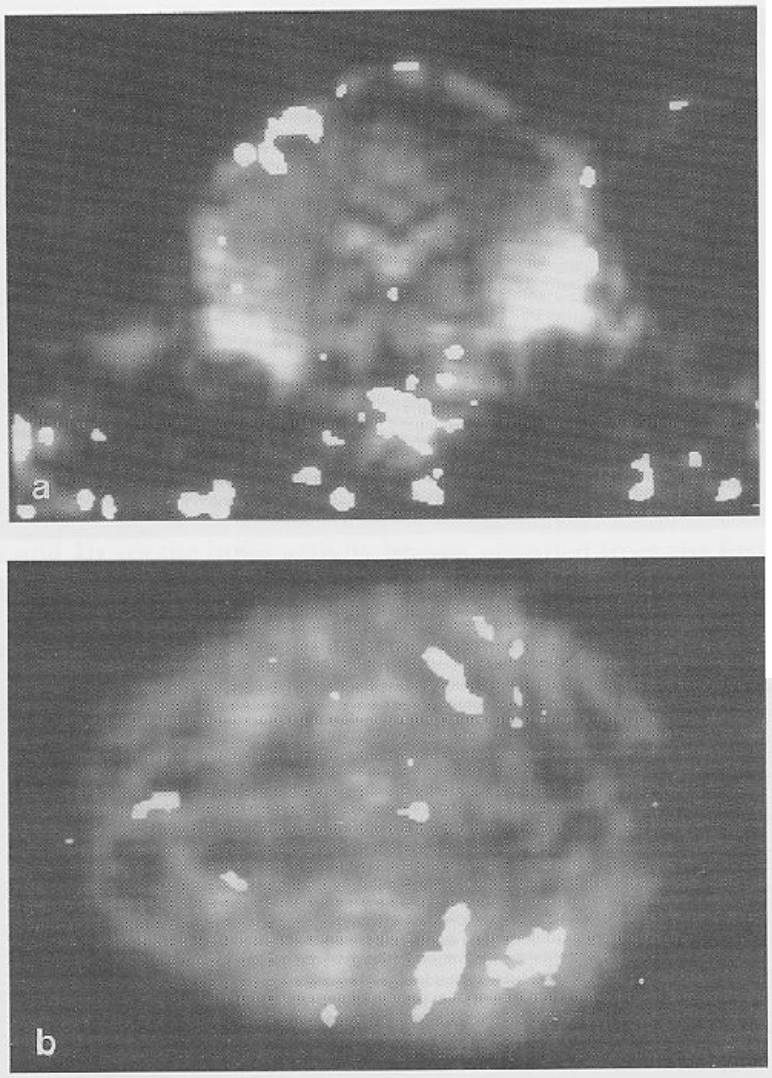
TR = 2 sec
TE = 50 ms
One slice
In plane 3.75 x 3.75

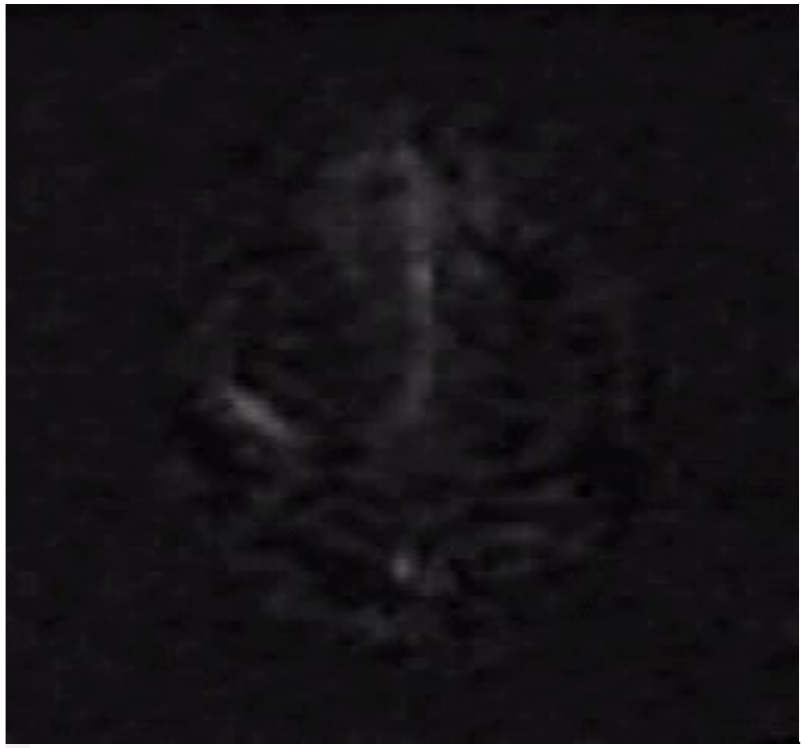
One little known fact…

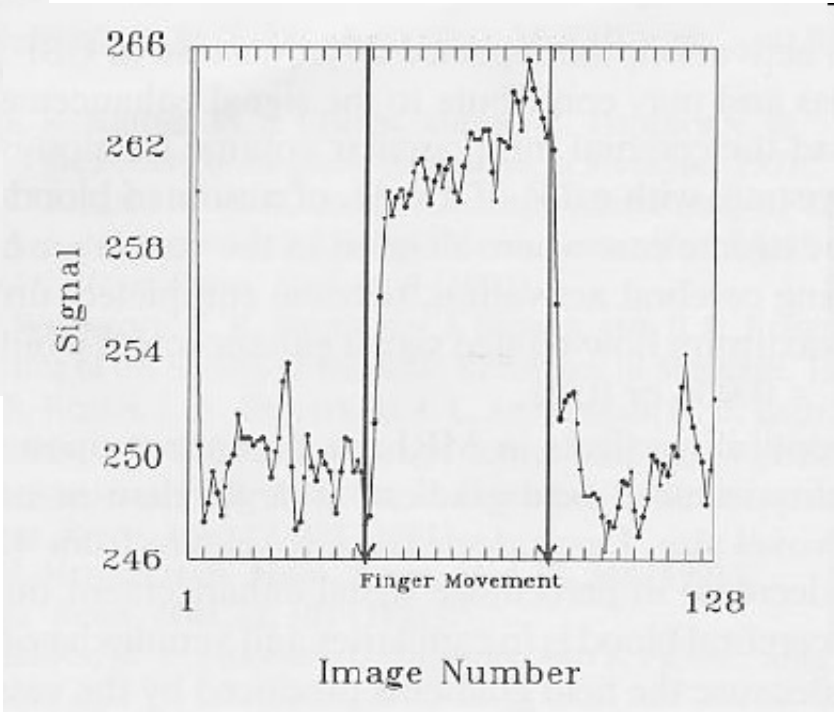
We didn't even need a gradient coil:

EPI at 5mm x 5mm x 5mm was quite possible using 100 amp gradient amplifiers and the whole body gradient coils…

Every scanner in the world in 1991 could have performed EPI-based fMRI at perfectly reasonable resolution.



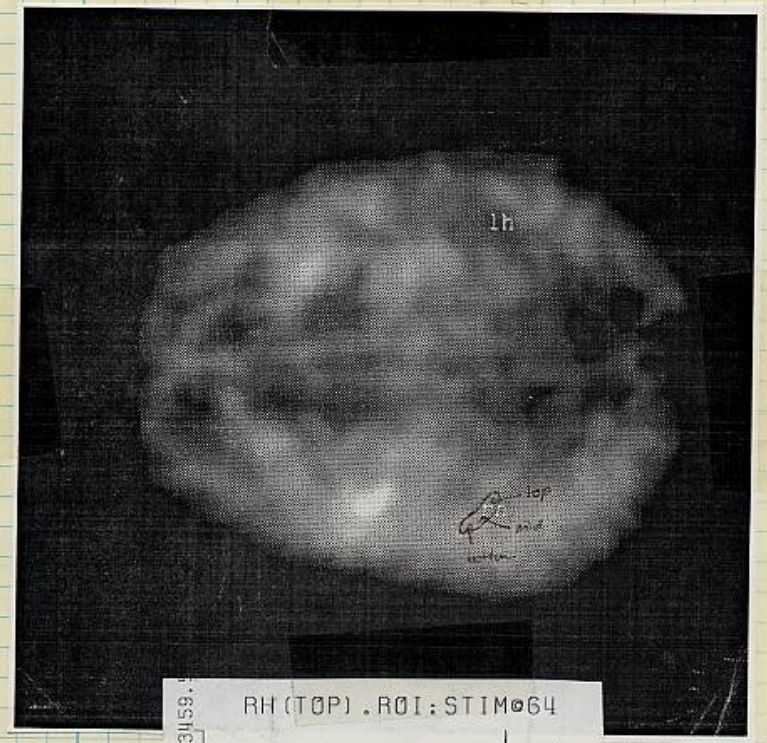


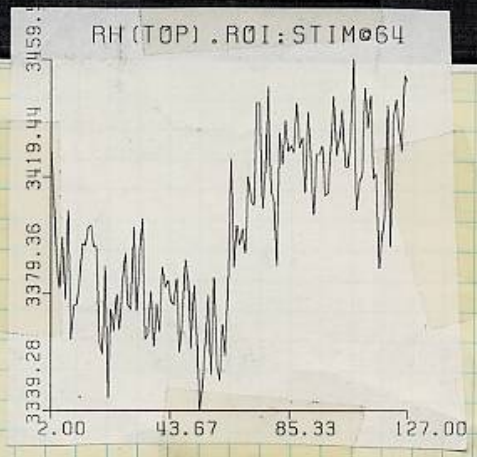


P. A. Bandettini, et al., (1992)
"Time course EPI of human brain function during task activation."
Magn. Reson. Med 25, 390-397.

9-16-91 Results from dH61 (Sig ↑ upon stim?!!)

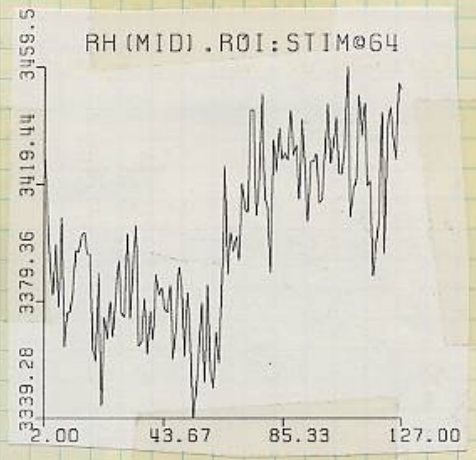
Experiment 1: Rest until G3 then move right fingers



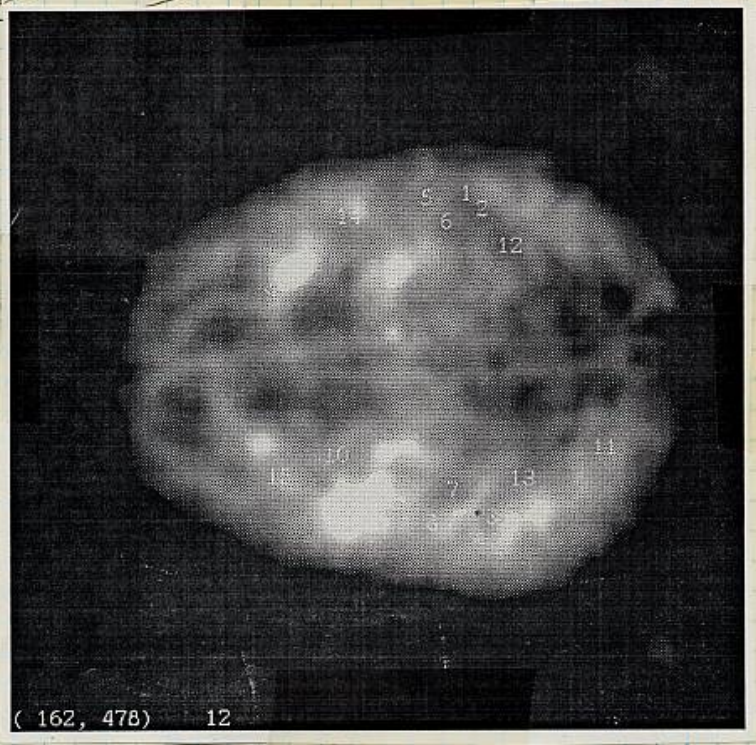


19

9-16-91



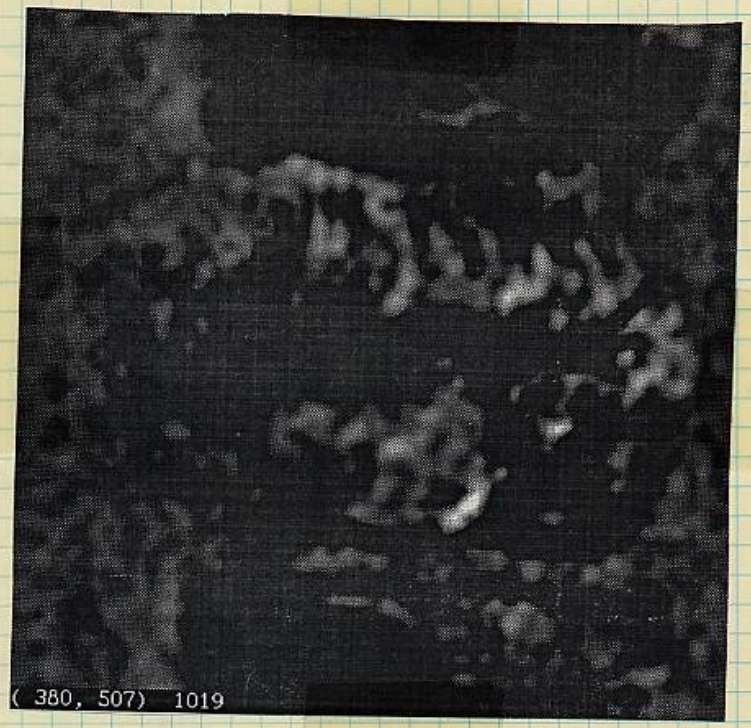
ROI's from p17



9-16-91

Finally, a difference image in which the average of the first 64 images (no movement) is subtracted from the last 64 images (movement) of right hand.

Right-Hand Movement



Resolution.
20 cm / 64
.3125 cm
= 3.125 mm

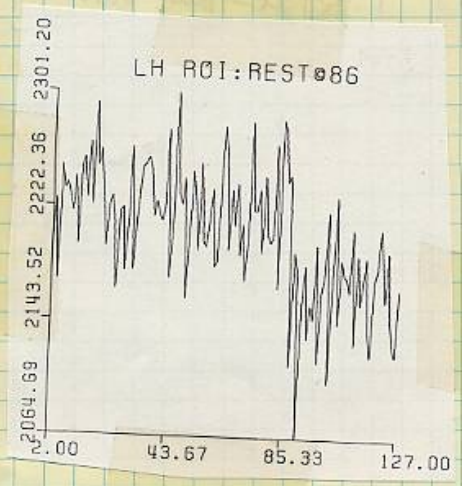
Brightest area is an indicator of largest signal increase when the right hand was stimulated (fingers moved) → exactly corresponds to region of motor cortex and sensory and supplimentary motor cortex as well that is associated with right hand movement

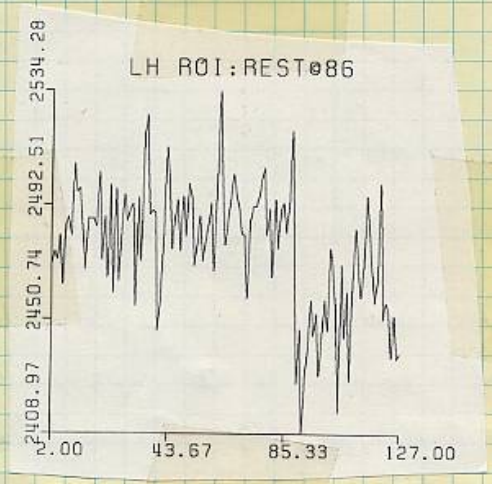
9-16-91

Results from experiment #2

Experiment #2 consisted of moving the left hand and then stopping the movement after 86 images.

LH ROI from p16





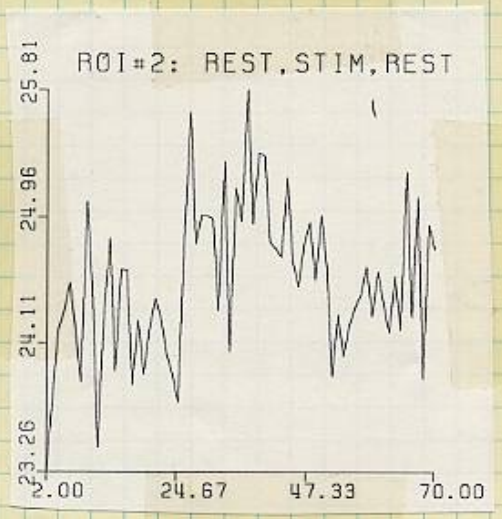
Trying to figure out the basic mechanism.

24

9-16-91

Experiment #3

Rest for 24 images, Move both hands for 24, then rest For 24.

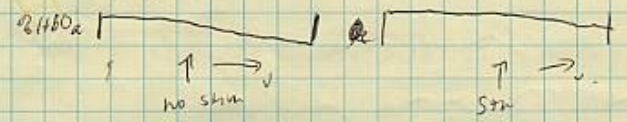


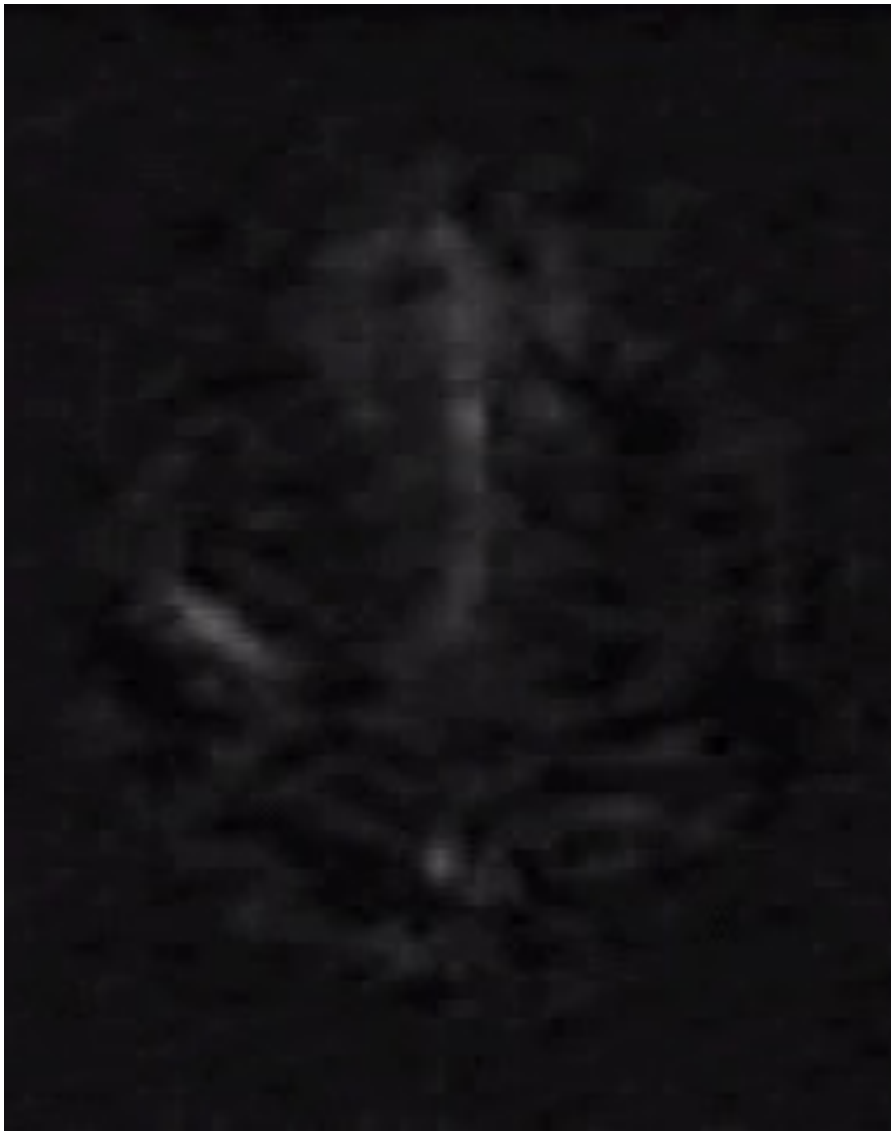
Rough Theory of What is going on here:

Stim nerve → move hand → ↑CO_2 ↑HT ↓O_2 in tissue → capillary and vein dilation → ↑ Blood flow → ↓% deoxy at stim

↑ signal due to ↓ susceptibility ← Stop stim ← ↑O_2 ↓CO_2 ↓HT in tissue ← vasoconstriction + Cap. ← decreased blood flow ← ↑% deoxyHb at steady state

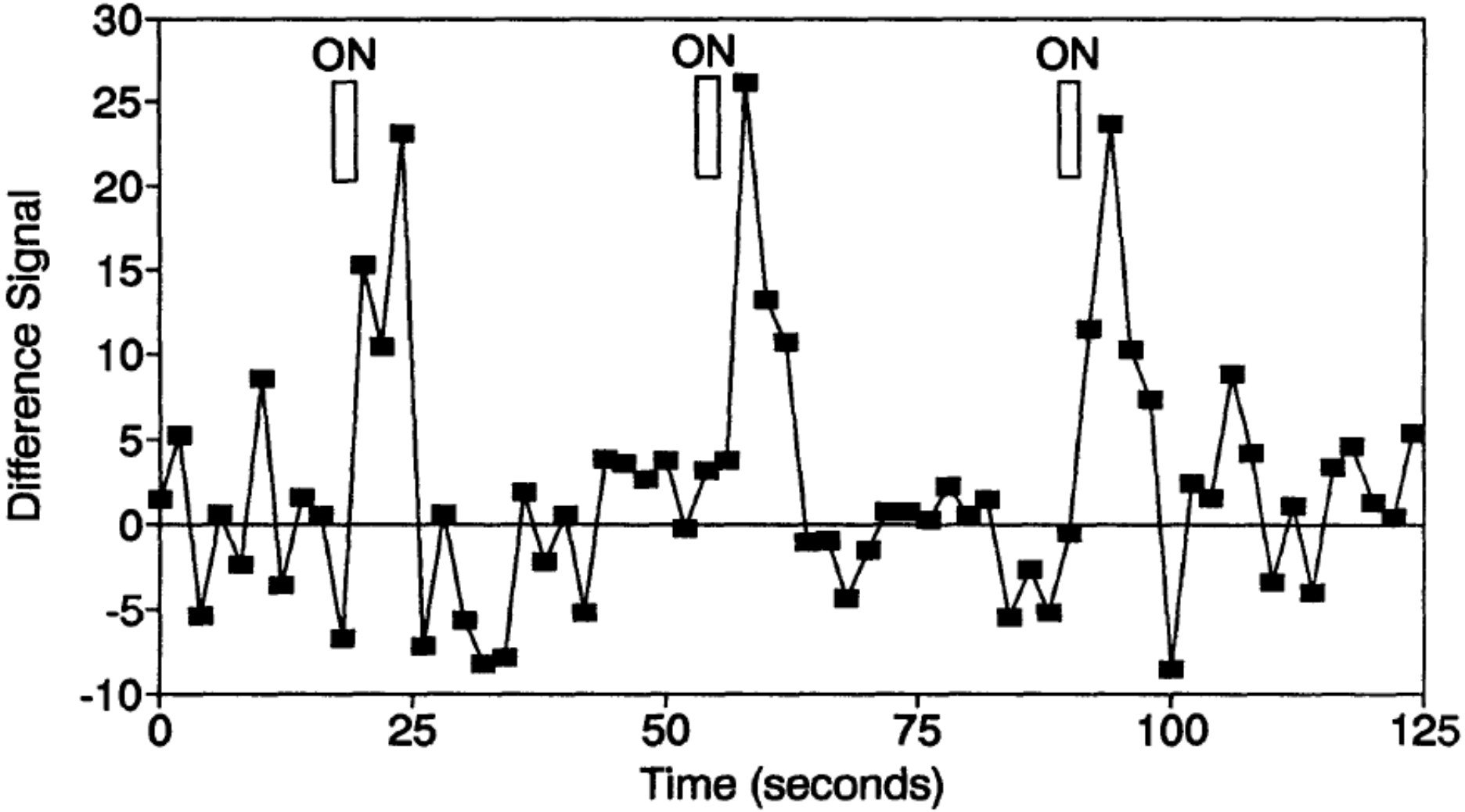
Question: Relationship between flow volume and bulk susceptability in capillaries.





1991

The first event-related studies.



Blamire, A. M., et al. (1992). "Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging." Proc. Natl. Acad. Sci. USA 89: 11069-11073.

1992…Perfusion using Arterial Spin Labeling

MAGNETIC RESONANCE IN MEDICINE 23, 37–45 (1992)

Perfusion Imaging

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Received July 2, 1990; revised January 3, 1991

Measurement of tissue perfusion is important for the functional assessment of organs *in vivo*. Here we report the use of ^{1}H NMR imaging to generate perfusion maps in the rat brain at 4.7 T. Blood water flowing to the brain is saturated in the neck region with a slice-selective saturation imaging sequence, creating an endogenous tracer in the form of proximally saturated spins. Because proton T_1 times are relatively long, particularly at high field strengths, saturated spins exchange with bulk water in the brain and a steady state is created where the regional concentration of saturated spins is determined by the regional blood flow and regional T_1. Distal saturation applied equidistantly outside the brain serves as a control for effects of the saturation pulses. Average cerebral blood flow in normocapnic rat brain under halothane anesthesia was determined to be 105 ± 16 cc · 100 g^{-1} · min^{-1} (mean ± SEM, $n = 3$), in good agreement with values reported in the literature, and was sensitive to increases in arterial pCO_2. This technique allows regional perfusion maps to be measured noninvasively, with the resolution of ^{1}H MRI, and should be readily applicable to human studies.

1992…Perfusion using Arterial Spin Labeling

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 212–216, January 1992
Biophysics

Magnetic resonance imaging of perfusion using spin inversion of arterial water

(cerebral blood flow/adiabatic fast passage/hypercarbia/rat brain/cold injury)

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*Pittsburgh Nuclear Magnetic Resonance Center for Biomedical Research, and §Department of Biological Sciences, Carnegie Mellon University, Pittsburgh, PA 15213; and †Metabolic Magnetic Resonance Research Center, Department of Radiology, and ‡Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104

Communicated by Mildred Cohn, September 19, 1991

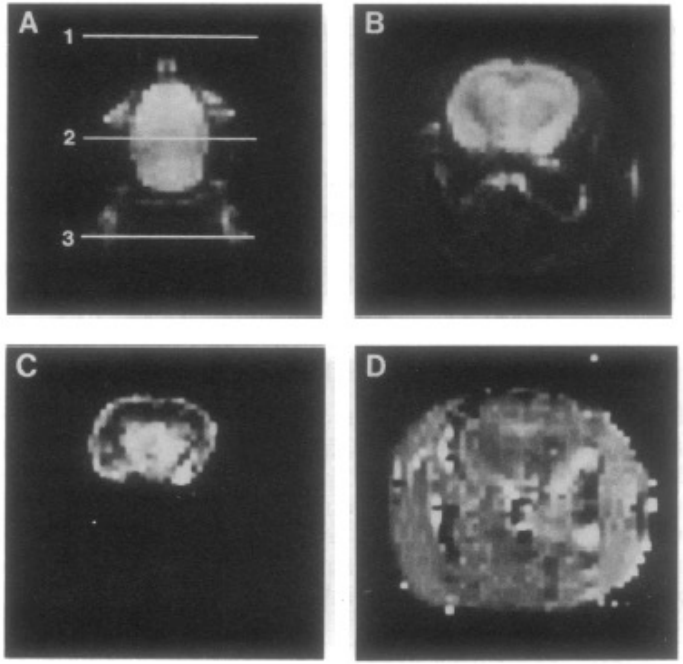


FIG. 2. (*A*) Coronal image of a rat head. The resonance planes for radiofrequency used for spin inversion by AFP for control and inversion images are indicated by 1 and 3, respectively, and plane 2 is the detection plane. (*B*) Control transverse image from the detection plane (plane 2 in *A*). (*C*) Difference image between control and inversion images. (*D*) T_{1app} image.

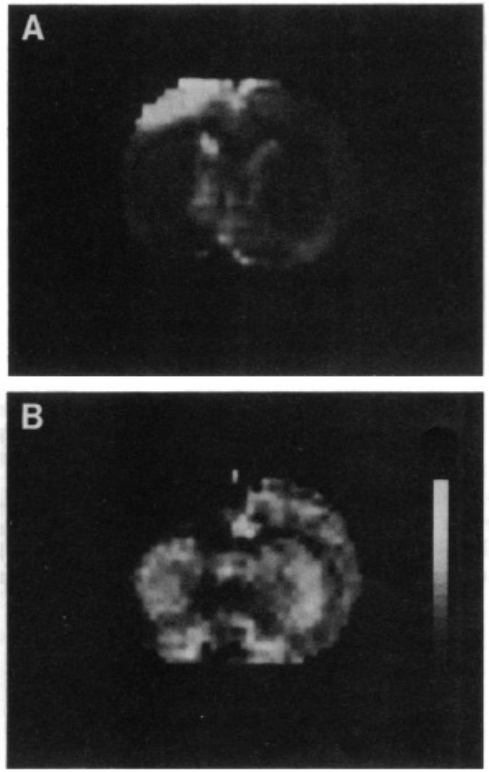
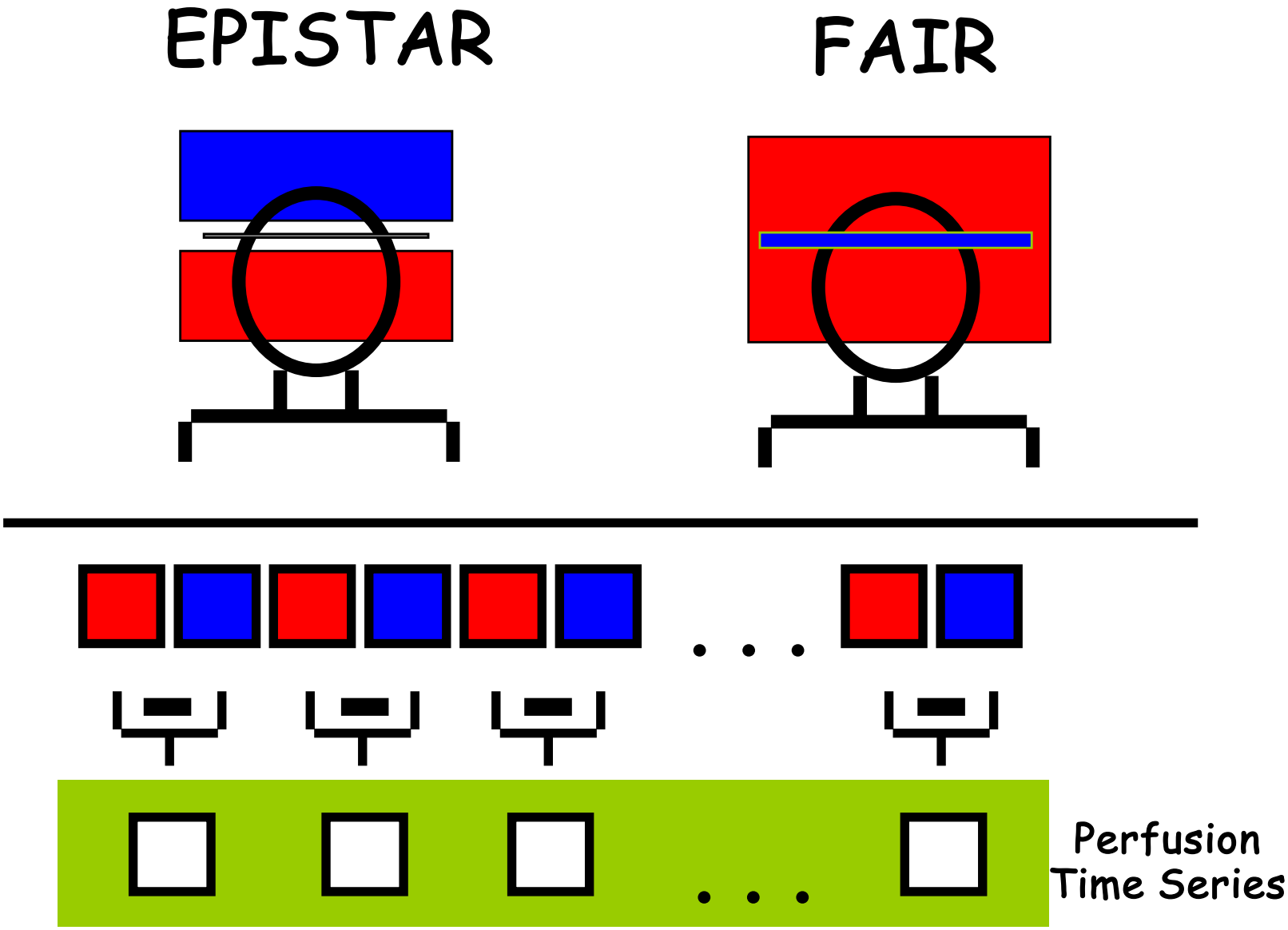
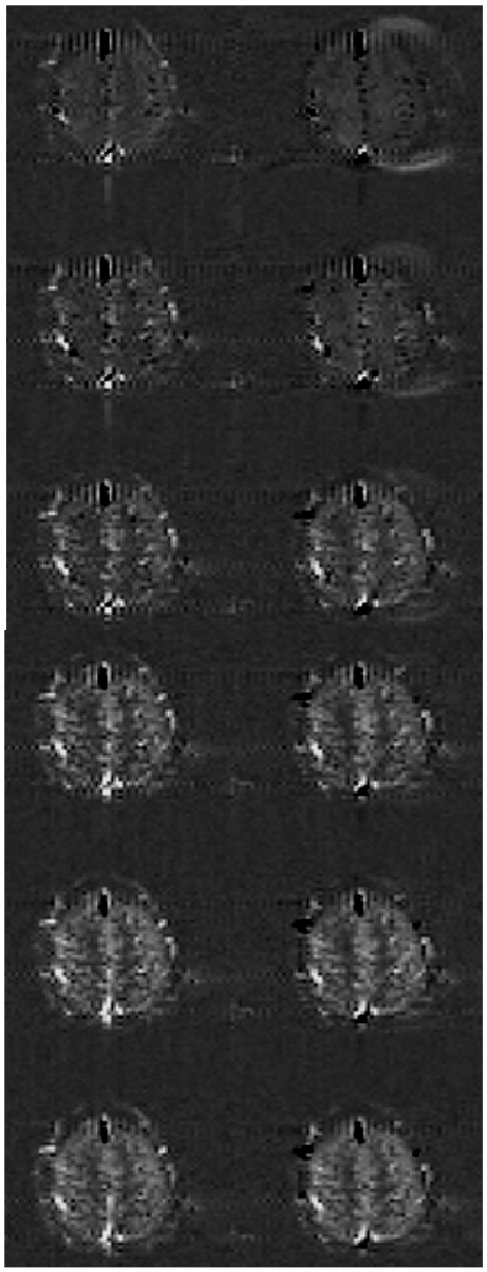


FIG. 5. Comparison of conventional MRI and perfusion imaging of a rat brain subjected to a regional cold injury. (*A*) Conventional T_2-weighted image (TE = 60 ms, TR = 2 s). The injured region shows up as hyperintensity due to a longer T_2. (*B*) Perfusion image of the same slice. The grey scale is from 0 to 6 $ml \cdot g^{-1} \cdot min^{-1}$. The injured region is dark due to low flow.

Perfusion Contrast



TI (ms)	FAIR	EPISTAR
200		
400		
600		
800		
1000		
1200		

- **K. K. Kwong, et al, (1992)** "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation." **Proc. Natl. Acad. Sci. USA. 89, 5675-5679.**

- **S. Ogawa, et al., (1992)** "Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging." **Proc. Natl. Acad. Sci. USA. 89, 5951-5955.**

- **P. A. Bandettini, et al., (1992)** "Time course EPI of human brain function during task activation." **Magn. Reson. Med 25, 390-397.**

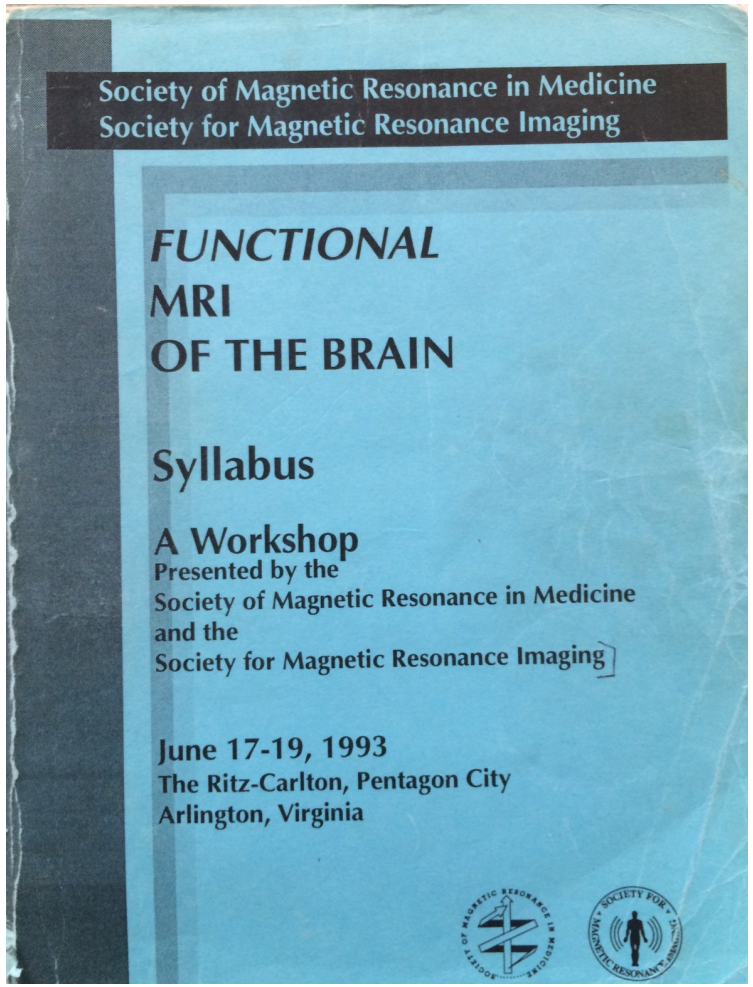
- **Blamire, A. M., et al. (1992).** "Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging." **Proc. Natl. Acad. Sci. USA 89: 11069-11073.**

- **Frahm, J., et al (1992)** "Dynamic MR Imaging of Human Brain Oxygenation During Rest and Photic-Stimulation." **Journal of Magnetic Resonance Imaging, 2, 501-505.**

Functional MRI of the Brain

A Report on the SMRM/SMRI Workshop held in Arlington, Virginia June 17–19, 1993

MRM 30:405–408 (1993)



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A proposed acronym...

Functional Neuroimaging with EPI: Sequence Issues

Robert Turner, Peter Jezzard, #Lucie Hertz-Pannier, #Denis Le Bihan, *David Feinberg

Laboratory of Cardiac Energetics, National Heart, Lung, and Blood Institute, and #Diagnostic Radiology Department, Clinical Center, NIH, Bethesda, MD 20892
*Department of Radiology, NYU Medical Center, New York, NY

ABSTRACT

Freedom from motion artifact, comparatively good SNR, rapid multi-slice capability, and excellent time resolution make Echo-Planar Imaging an excellent choice for BOLD contrast MR functional neuroimaging. However, when the gradient echo version of EPI is used for this purpose, problems arise regarding image quality and interpretation. Large draining veins distant from active neural regions are the major confusing factor. At high enough static magnetic fields, spin-echo EPI can be used to obtain images showing local changes of blood oxygenation related to brain activation, in which draining veins have less effect. The idea MRFN equence will combine gradient-recalled echo and spin echo features, and thus will be some variant of GRASE (GRAdient echo and Spin Echo).

A proposed acronym...

The earliest successful magnetic resonance functional neuroimaging (MRFN) studies with BOLD contrast were made using a gradient-echo version of echo-planar imaging (EPI). The EPI technique, proposed by Mansfield in 1977 (4), allows the capture of a complete MR image in under 100 ms. Thus most motions in the body are frozen and motion artifact rarely appears. EPI relies on a very rapidly switched magnetic field gradient of large amplitude, and a fast data capture rate. Since these features were not considered necessary by most manufacturers of commercial MR systems until recently, the technique has been available only in a few pioneering laboratories. The technique normally uses a full 90 degree rf pulse for spin excitation, and hence provides a comparatively high single-shot signal/noise ratio (SNR), considering the large receiver bandwidth required. For brain imaging, with equal voxel size, an EPI image with 40 ms acquisition time has been found to have the same SNR as a FLASH image with optimized bandwidth taking 2 seconds to acquire. Faster FLASH images will have a poorer SNR than EPI. Low flip-angle variants of EPI (5) can of course provide much higher values of SNR/unit time, though this sacrifices SNR in each

Functional Mapping of the Human Visual Cortex at 4 and 1.5 Tesla Using Deoxygenation Contrast EPI

R. Turner, P. Jezzard, H. Wen, K. K. Kwong, D. Le Bihan, T. Zeffiro, R. S. Balaban

MRM 29:277–279 (1993)

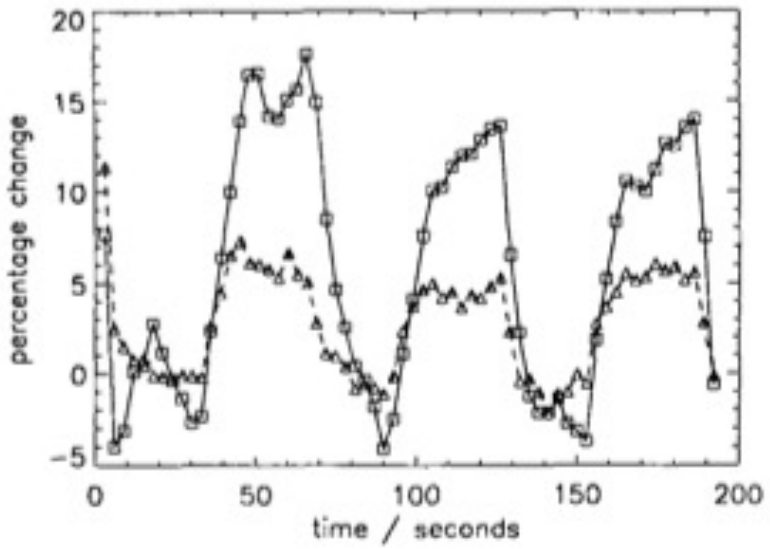
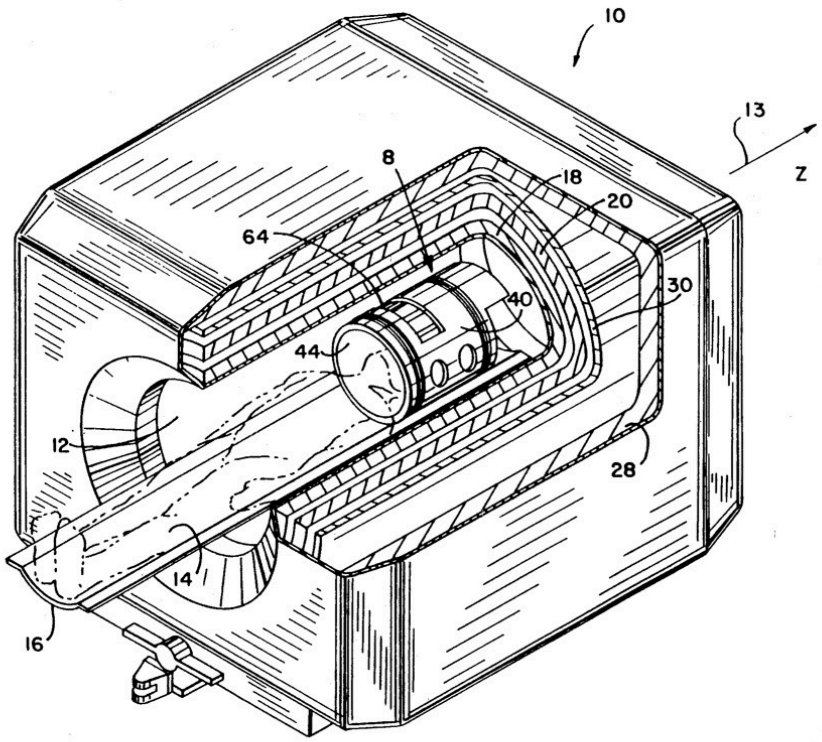


FIG. 2. Plot of fractional change in 4 T (squares) and 1.5 T (triangles) EPI image intensity versus time in the eight-voxel regions of interest in the visual cortex shown in Fig. 1, for a volunteer experiencing alternate 30-s periods of rest and photic stimulation. Details of acquisition for the 4 and 1.5 T data are described in the

Local Gradient Coil

FIG. 1



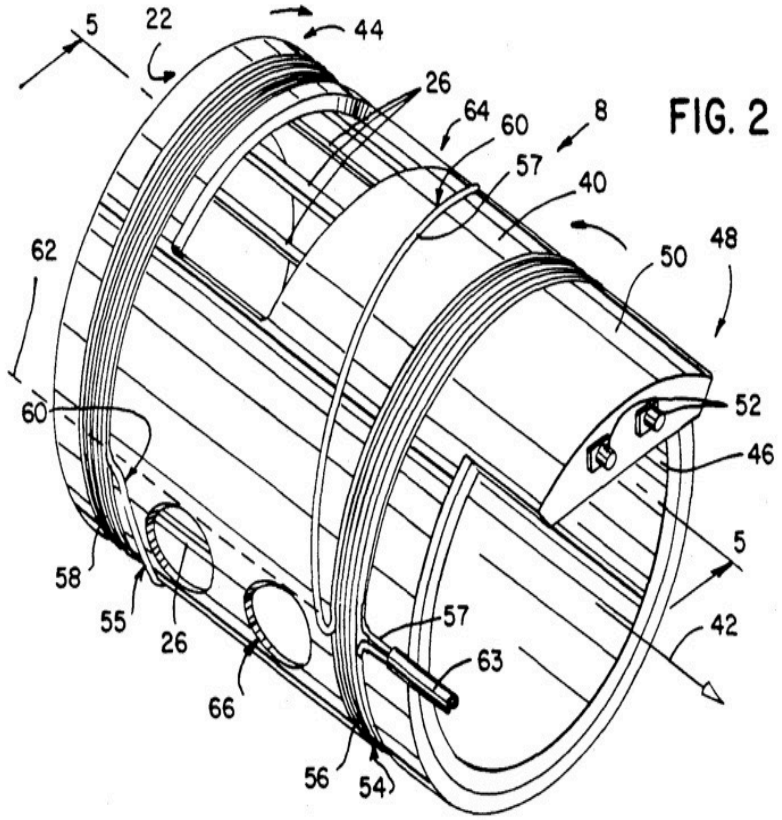
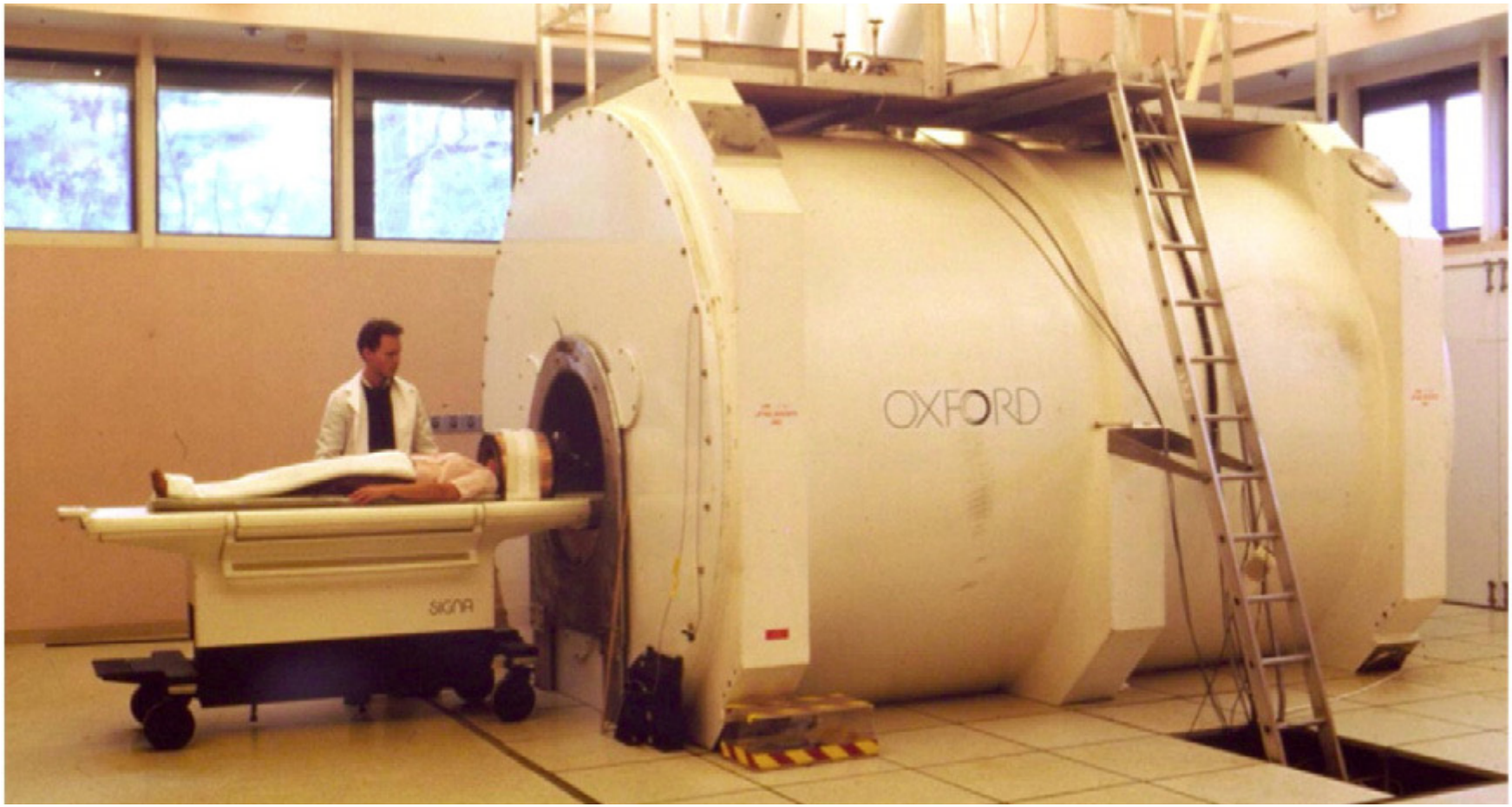


FIG. 2

NIH 4T

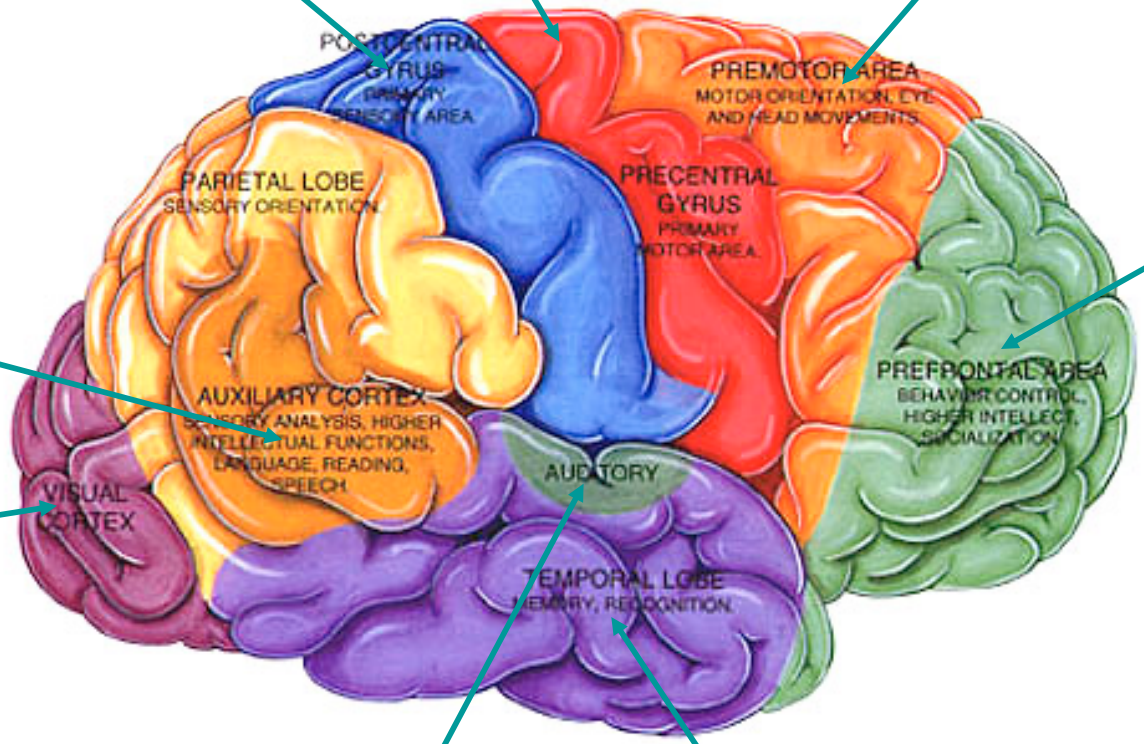


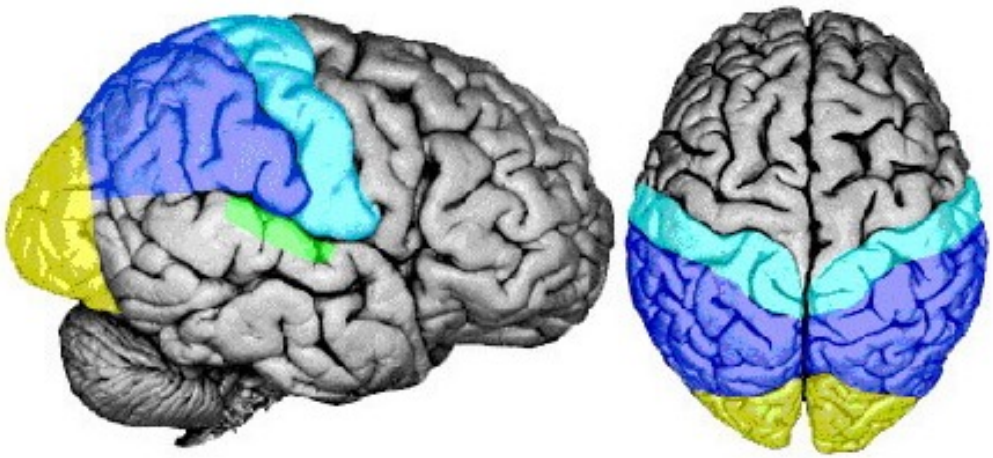
Siemens' new 7T

Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

Brain Function



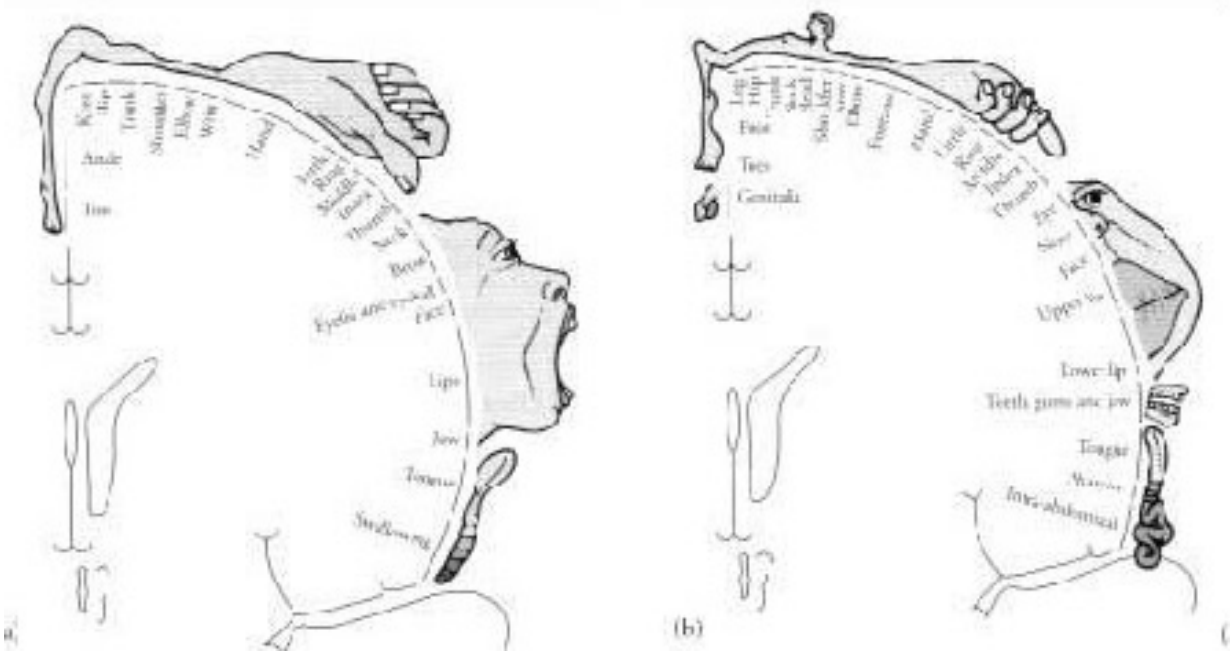


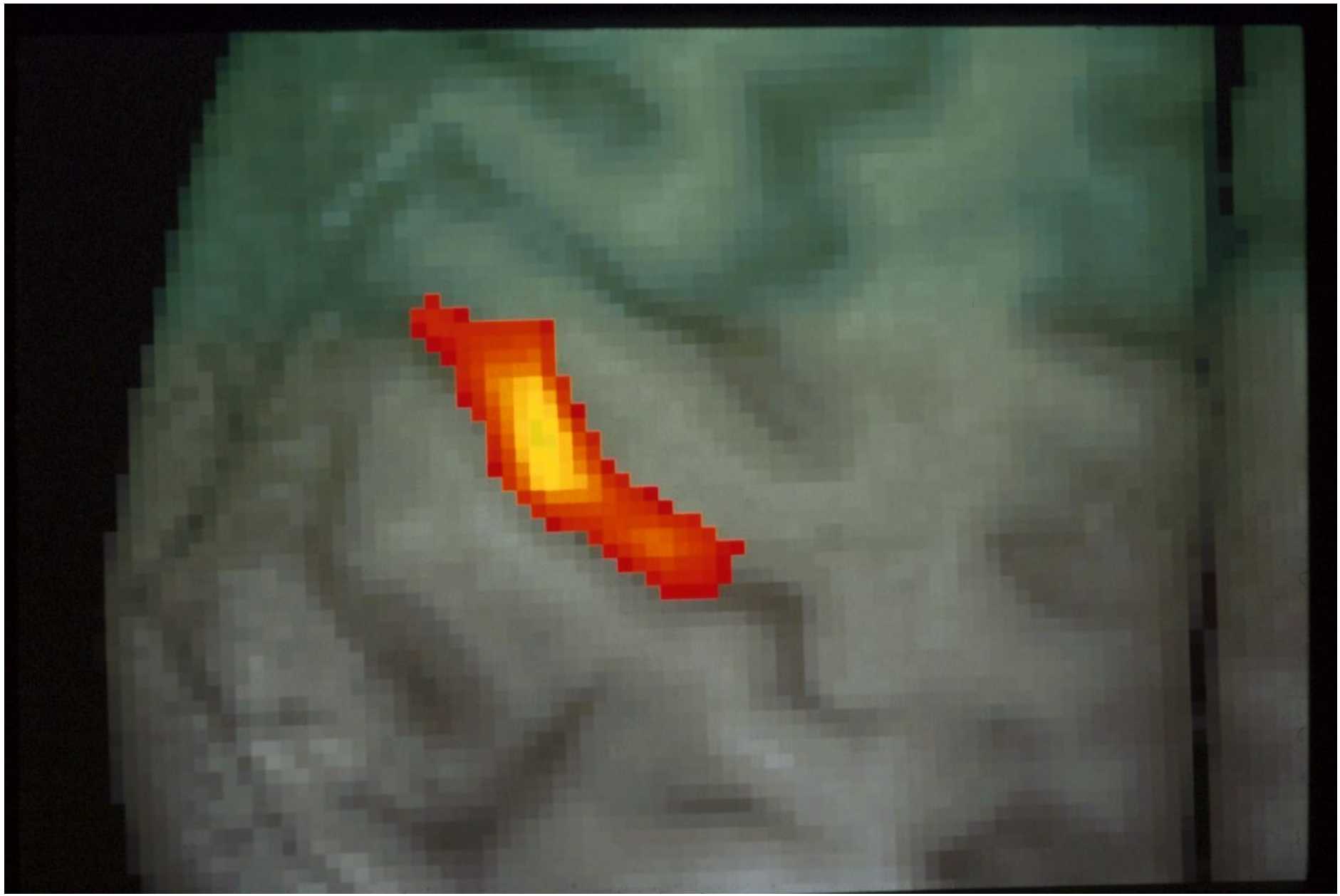
Parietal/
Somatosensory

Parietal/
Association Area

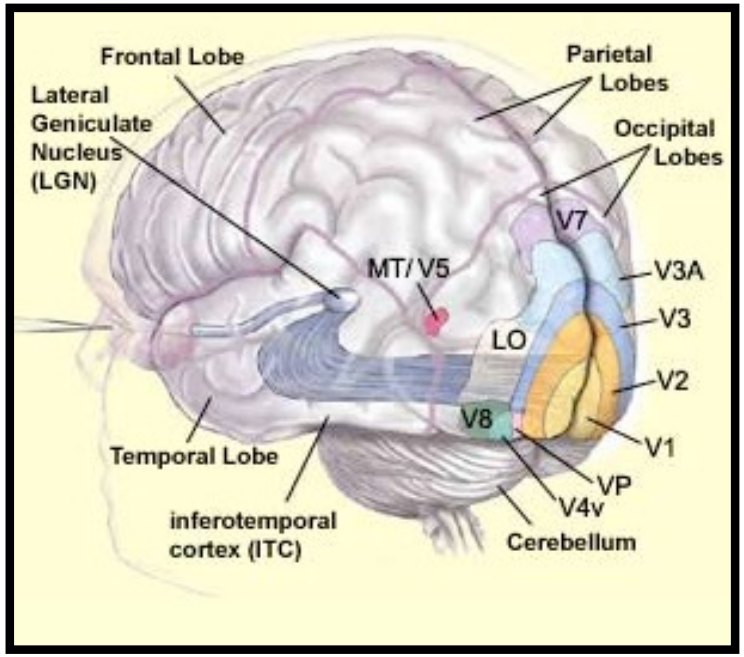
Occipital/Vision

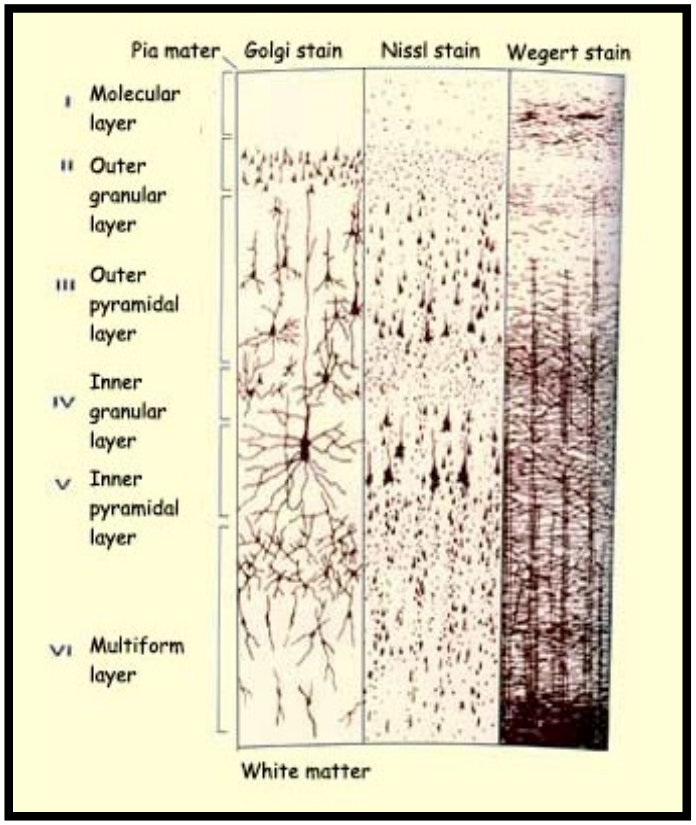
Auditory

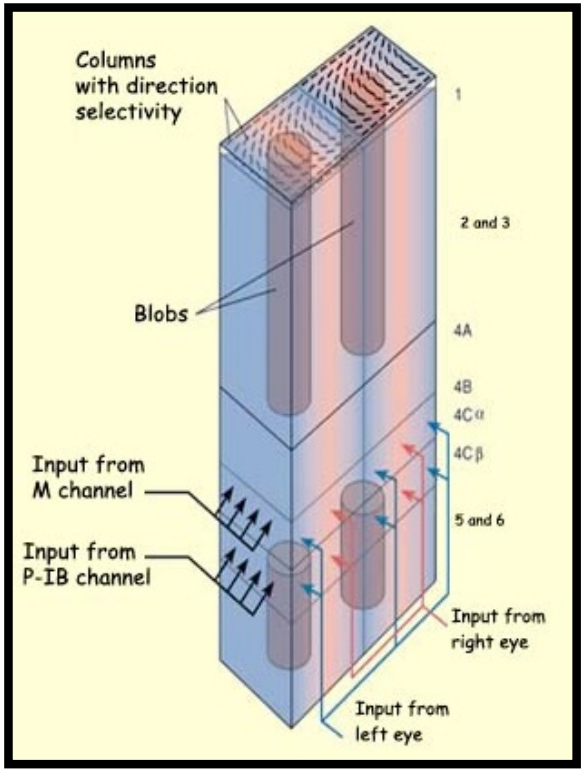




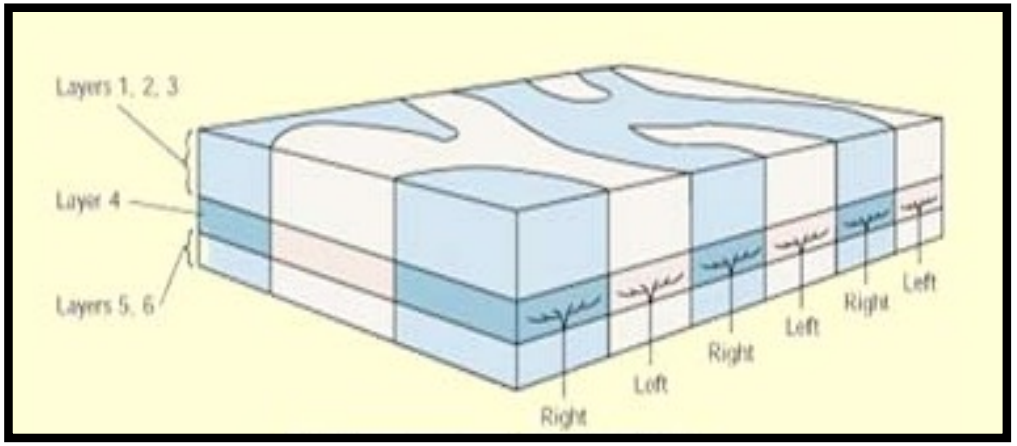
Visual Cortex Organization



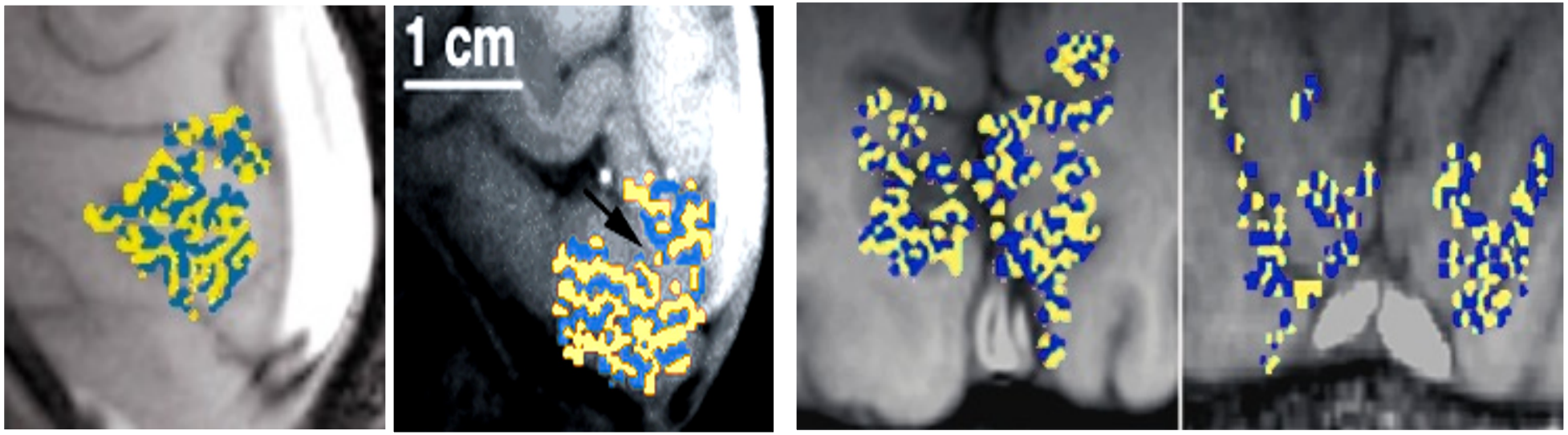




http://www.thebrain.mcgill.ca



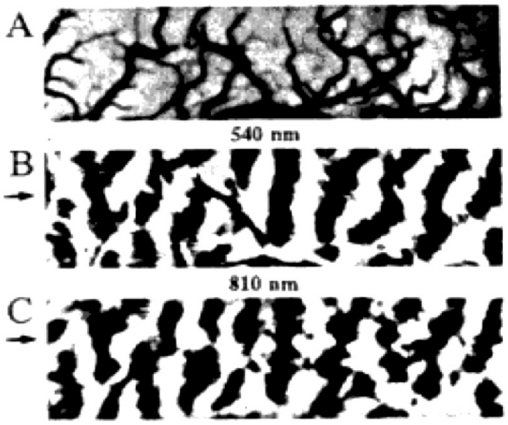
Ocular Dominance Column Mapping



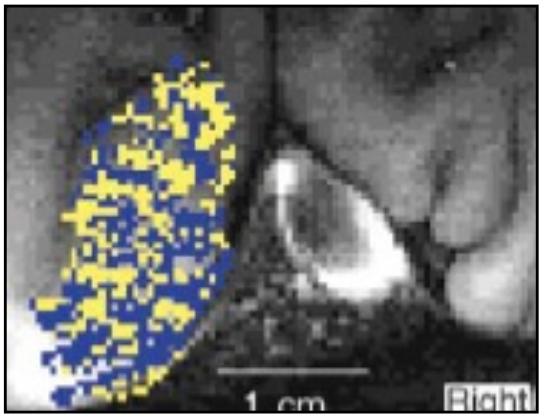
Menon, R. S., S. Ogawa, et al. (1997). J Neurophysiol 77(5): 2780-7.

0.54 x 0.54 in plane resolution

Optical Imaging

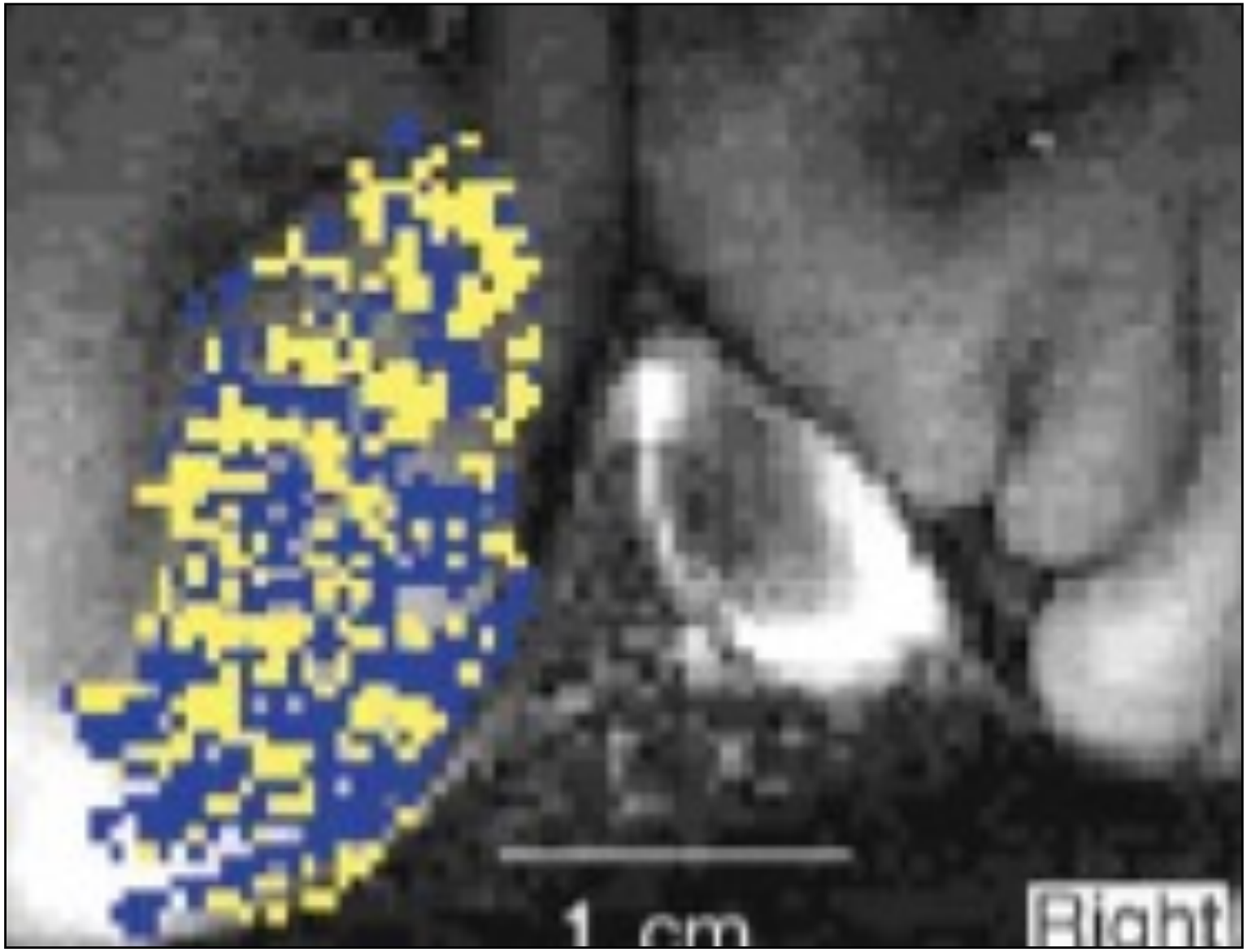


R. D. Frostig et. al, PNAS 87: 6082-6086, (1990).

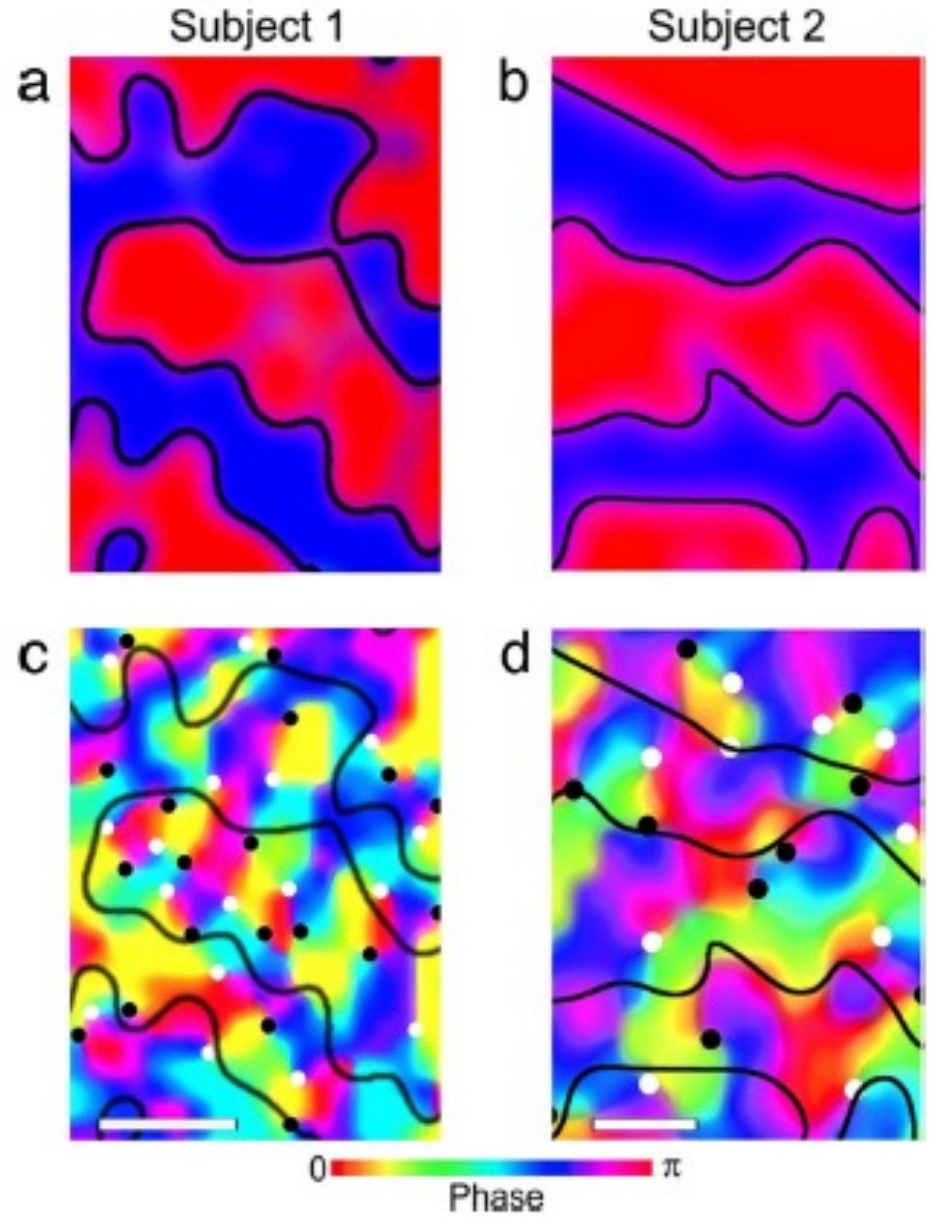


Cheng, et al. (2001) Neuron,32:359-374

0.47 x 0.47 in plane resolution

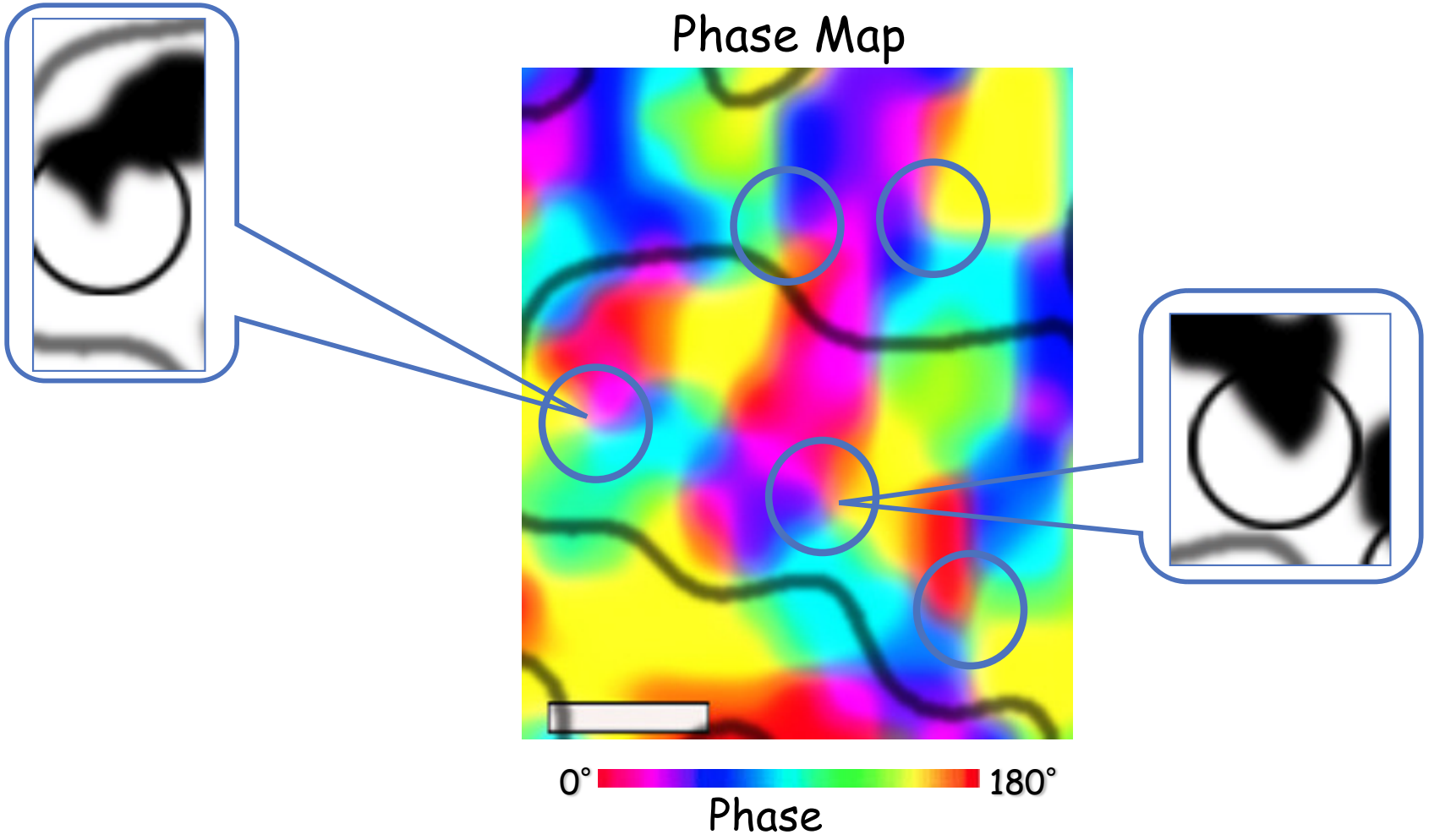


Cheng, et al. (2001) Neuron,32:359-374



Yacoub et al. PNAS 2008

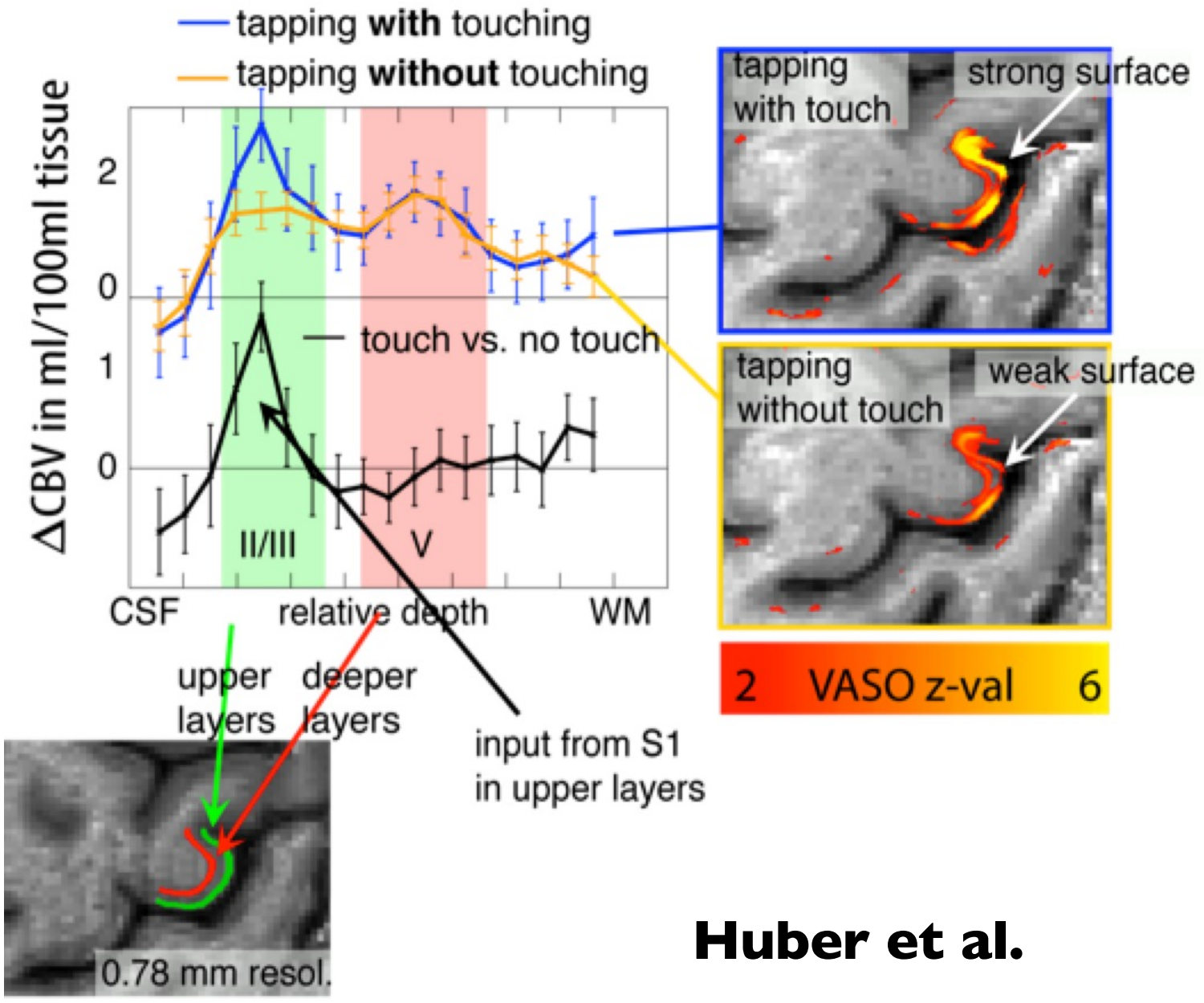
Orientation Columns in Human V1 as Revealed by fMRI at 7T



Scalebar = 0.5 mm

Yacoub et al. PNAS 2008

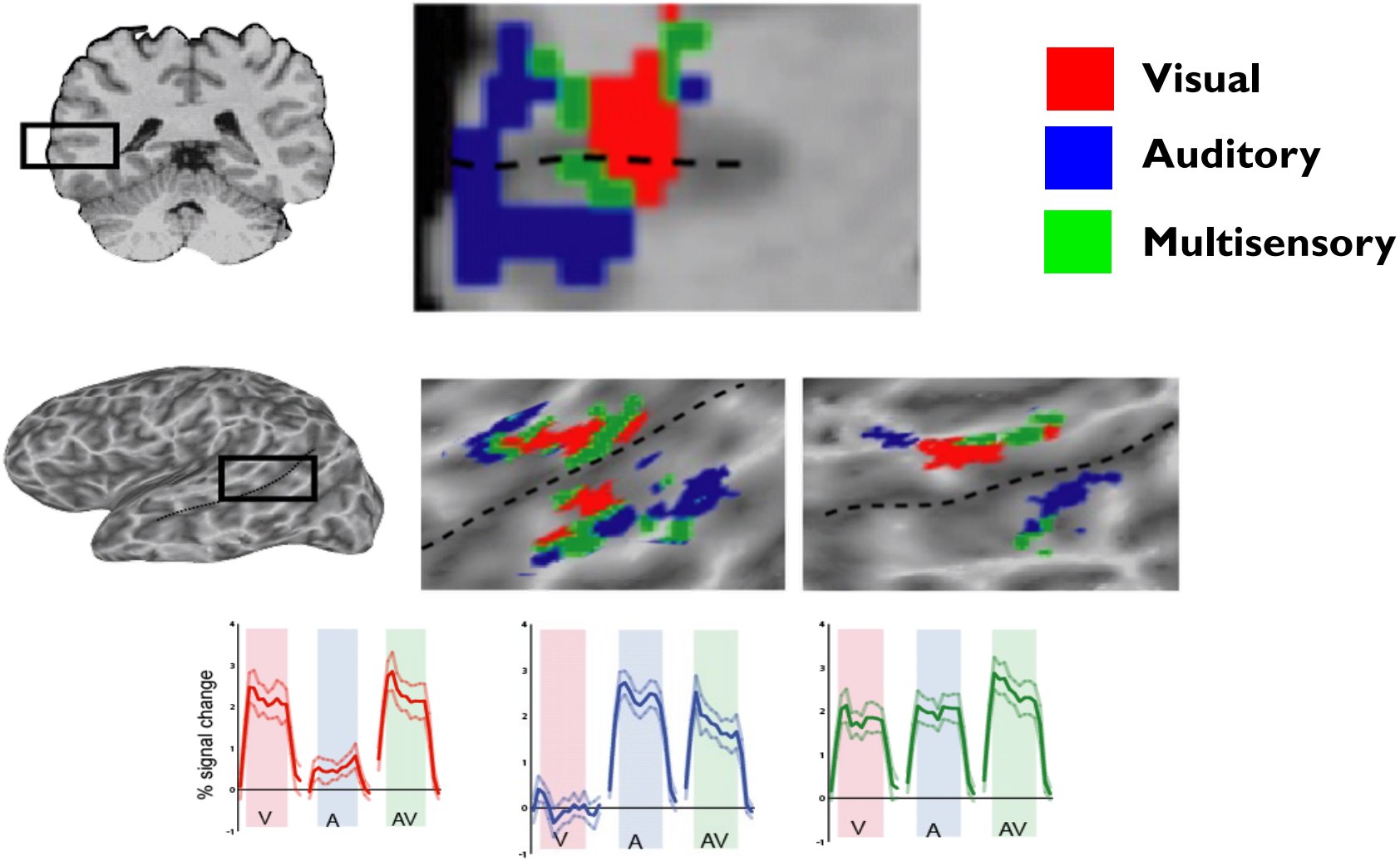
Layer Dependent Activity



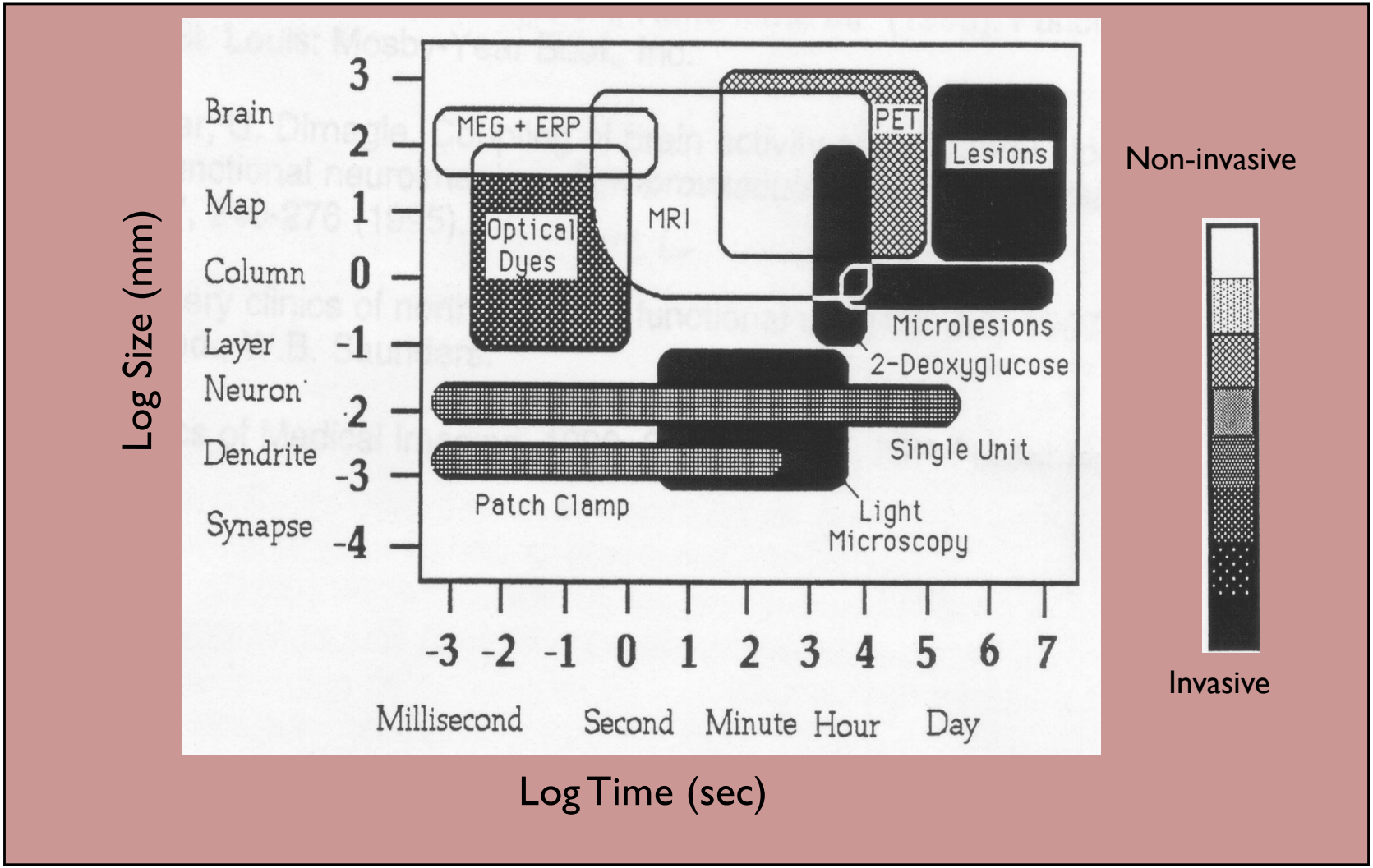
Huber et al.

Multi-sensory integration

M.S. Beauchamp et al.,



Functional Neuroimaging Techniques



after Churchland and Sejnowski, 1988

Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
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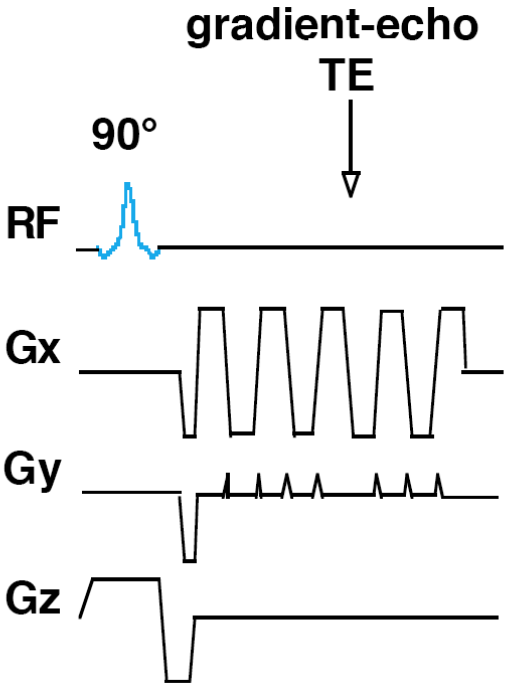
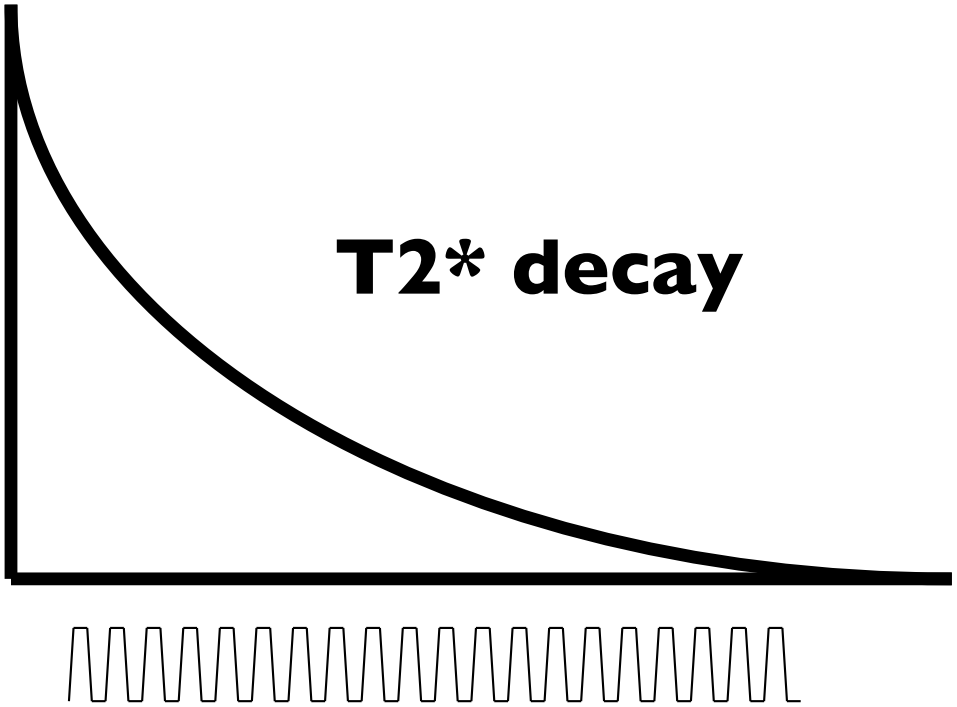
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

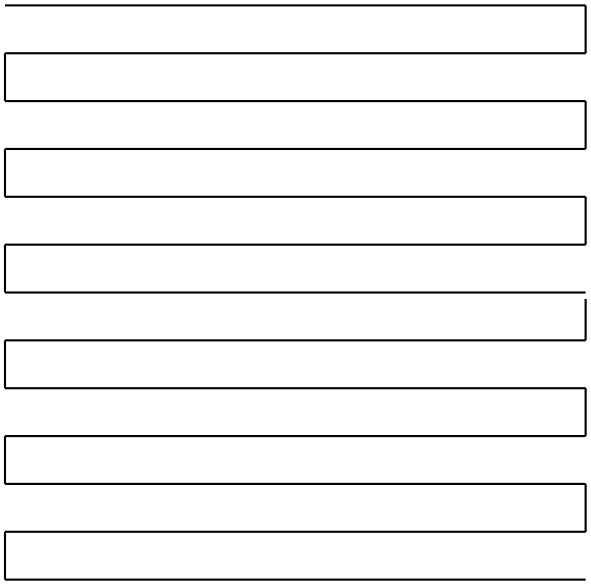
Single Shot Echo Planar Imaging (EPI)





EPI Readout Window

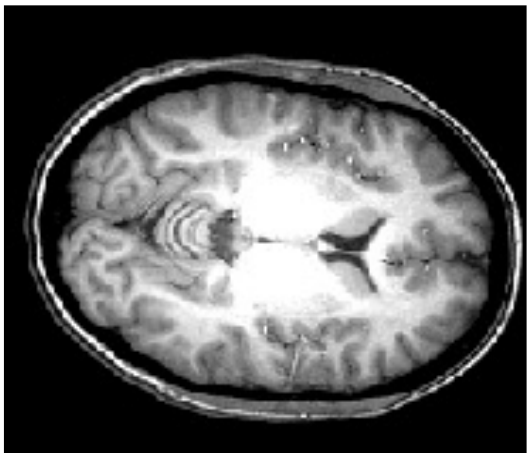
≈ 20 to 40 ms



MRI vs. fMRI

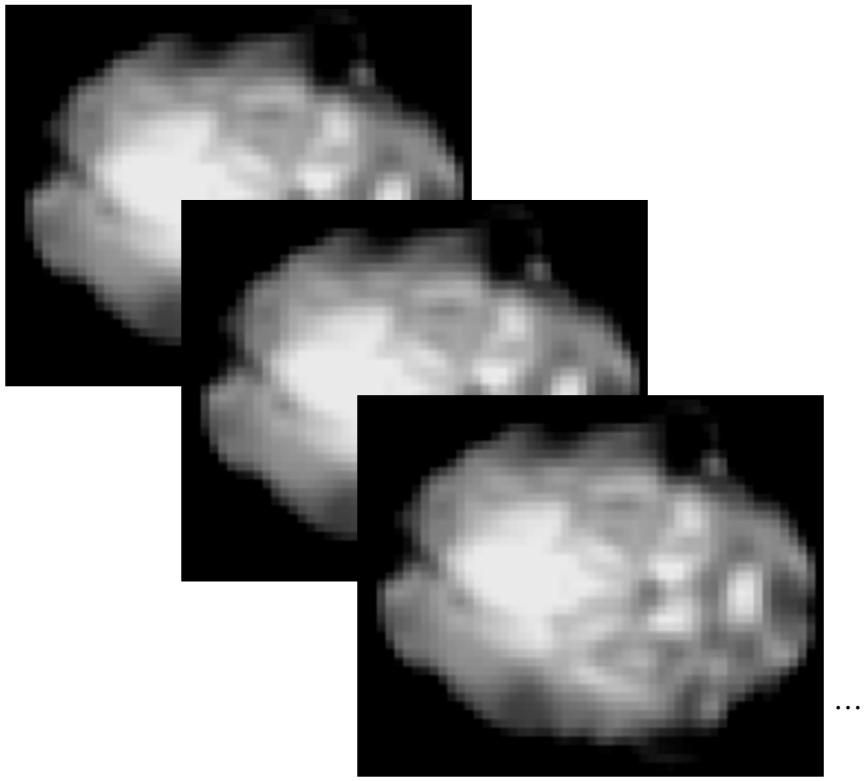
MRI

high resolution
(1 mm)



one image

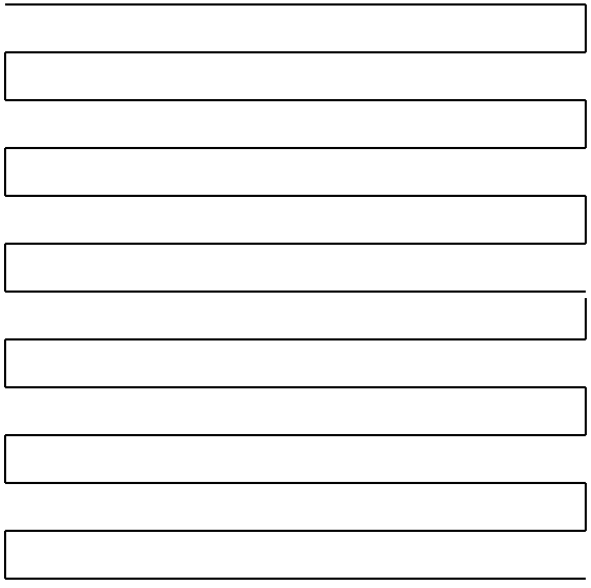
fMRI



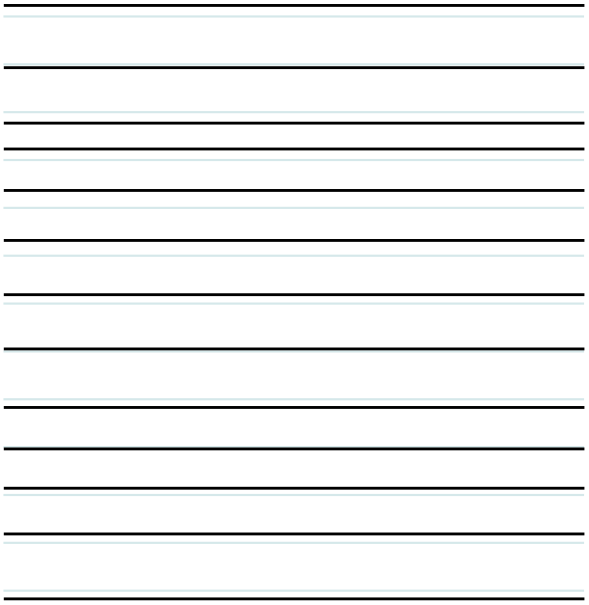
...

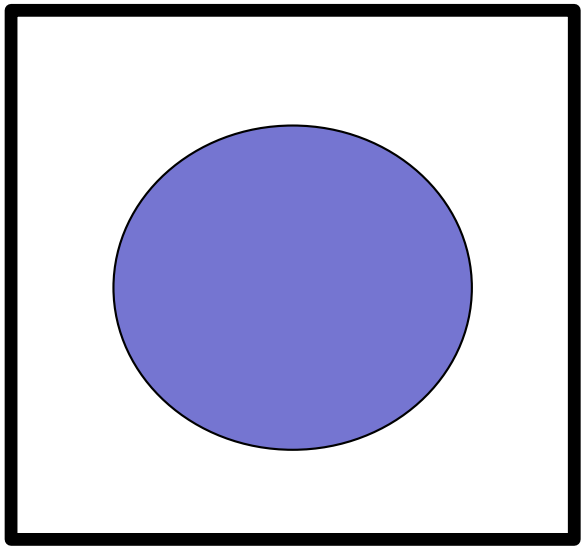
many images
(e.g., every 2 sec for 5 mins)

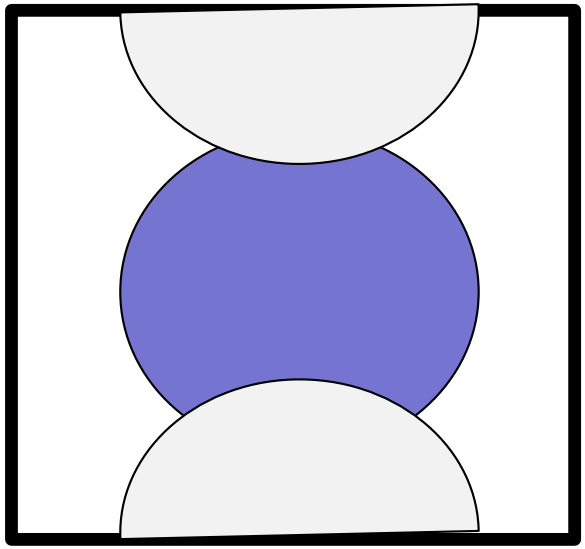
30 ms



10 sec
to
1 min





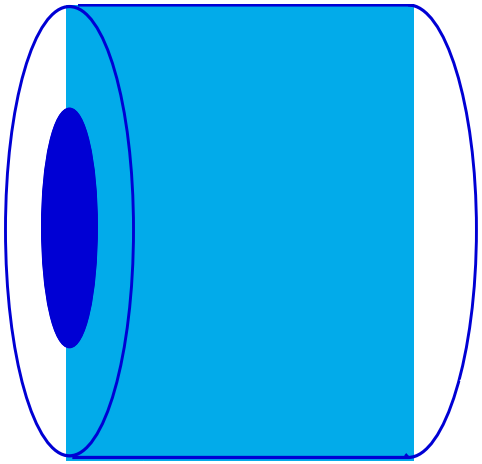


Approximate EPI Timeline

1976-84 P. Mansfield conceives of EPI
1989 EPI of humans emerges on a handful of scanners
3 x 3 x 3-10 mm^3
1989 ANMR retrofitted with GE scanners for EPI
1991 Home built head gradient coils perform EPI
1996 EPI is standard on clinical scanners
2000 Gradient performance continues to increase
2002 Parallel imaging allows for higher resolution EPI
2006 1.5 x 1.5 x 1.5 mm^3 single shot EPI possible
2009 At 7T sub – mm single shot EPI for fMRI is possible

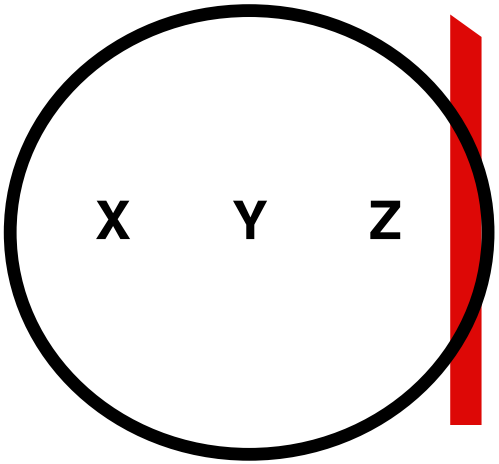
Imaging System Components

Magnet

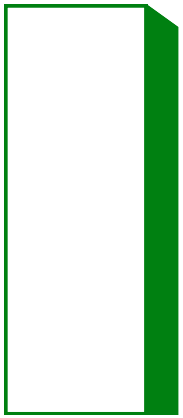


RF Receiver

Viewing Console

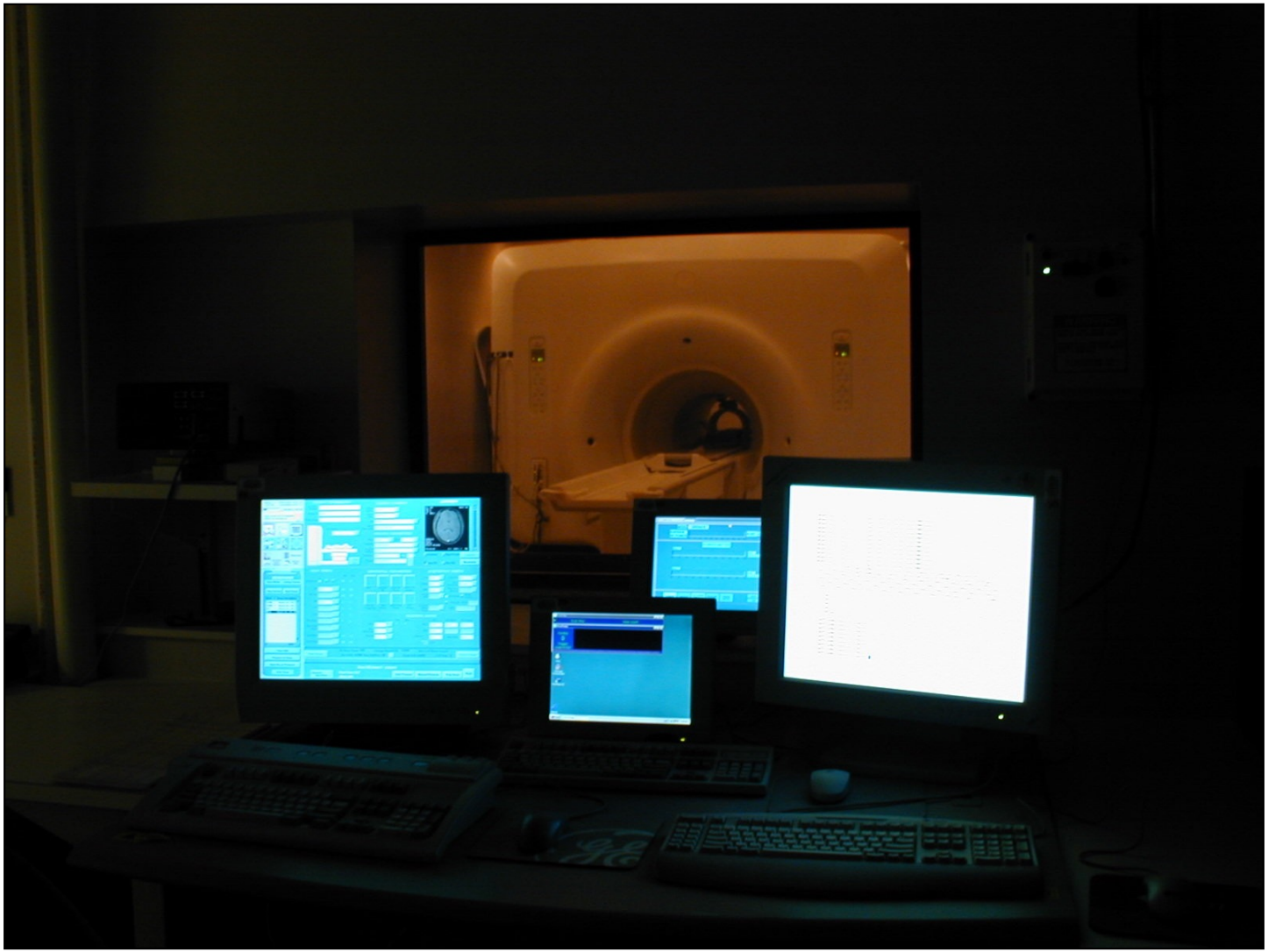


Gradient Power Systems



RF Transmitter

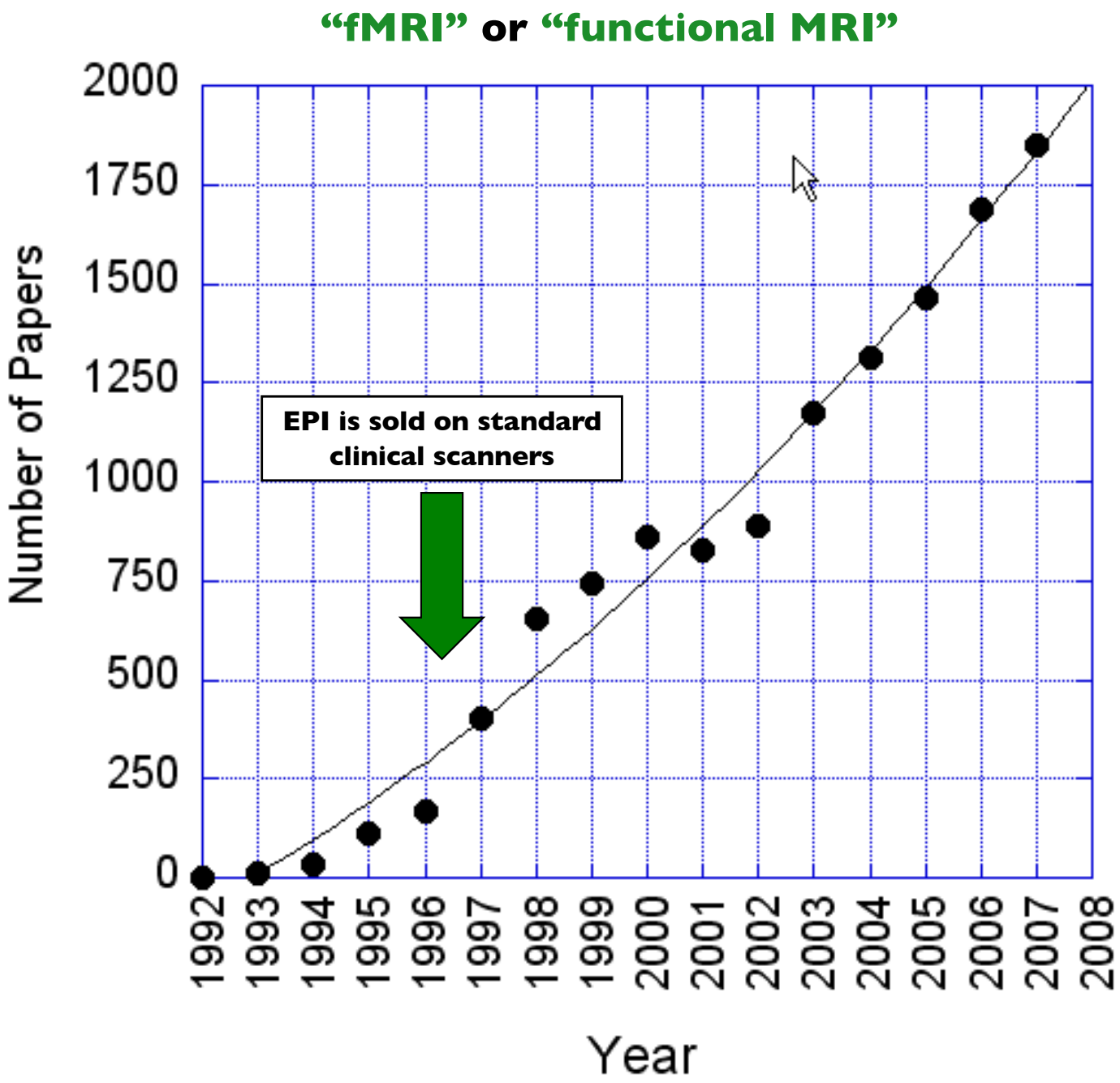
Scan Controller



Five Key Factors For The Emergence of Functional MRI

1. Magnetic properties of red blood cells
2. Activation related hemodynamic changes
3. Spatial scale of brain activation
4. Echo Planar Imaging
5. Prevalence of MRI scanners

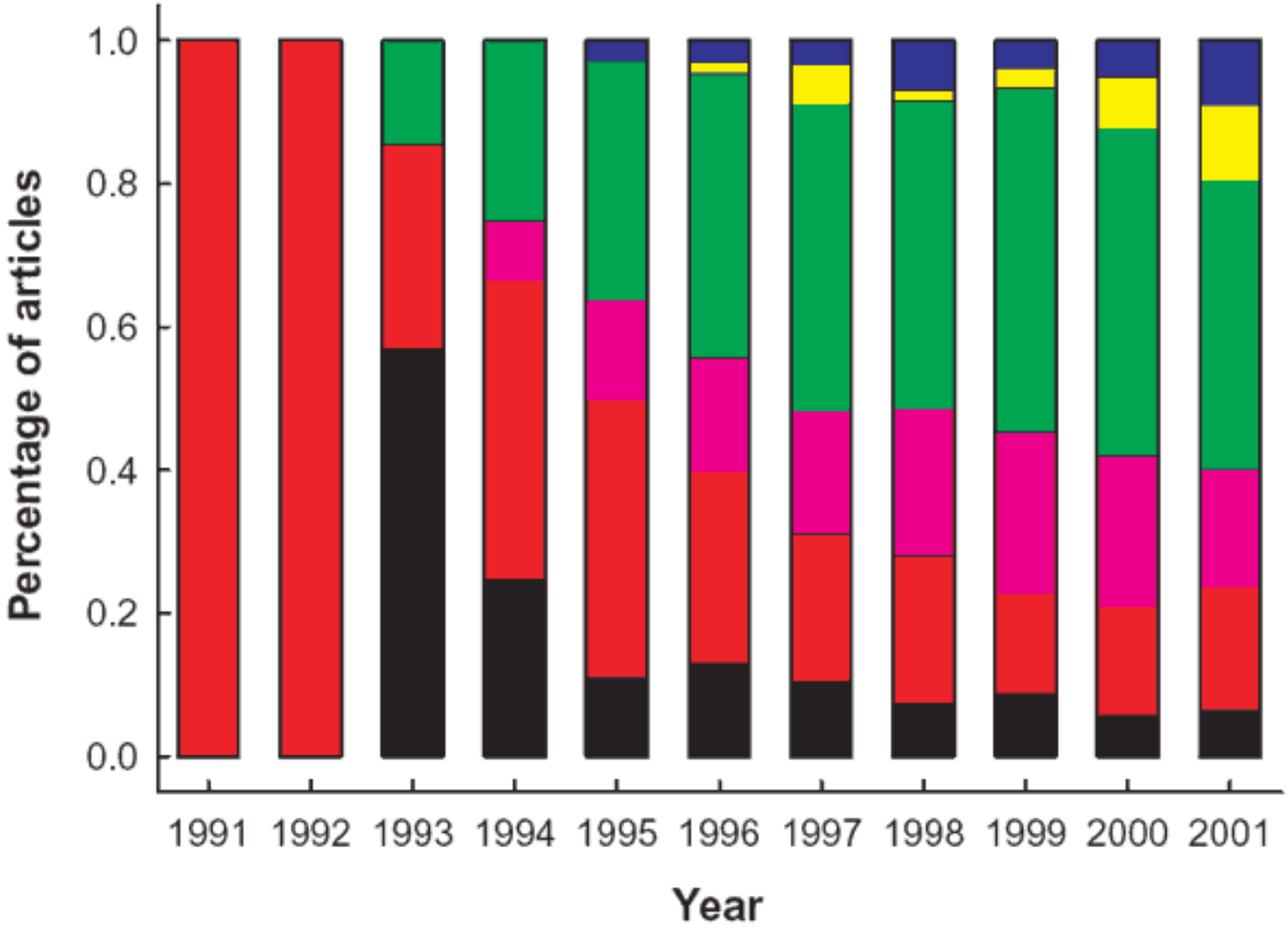
Scopus: Articles or Reviews Published per Year



How it all came together…

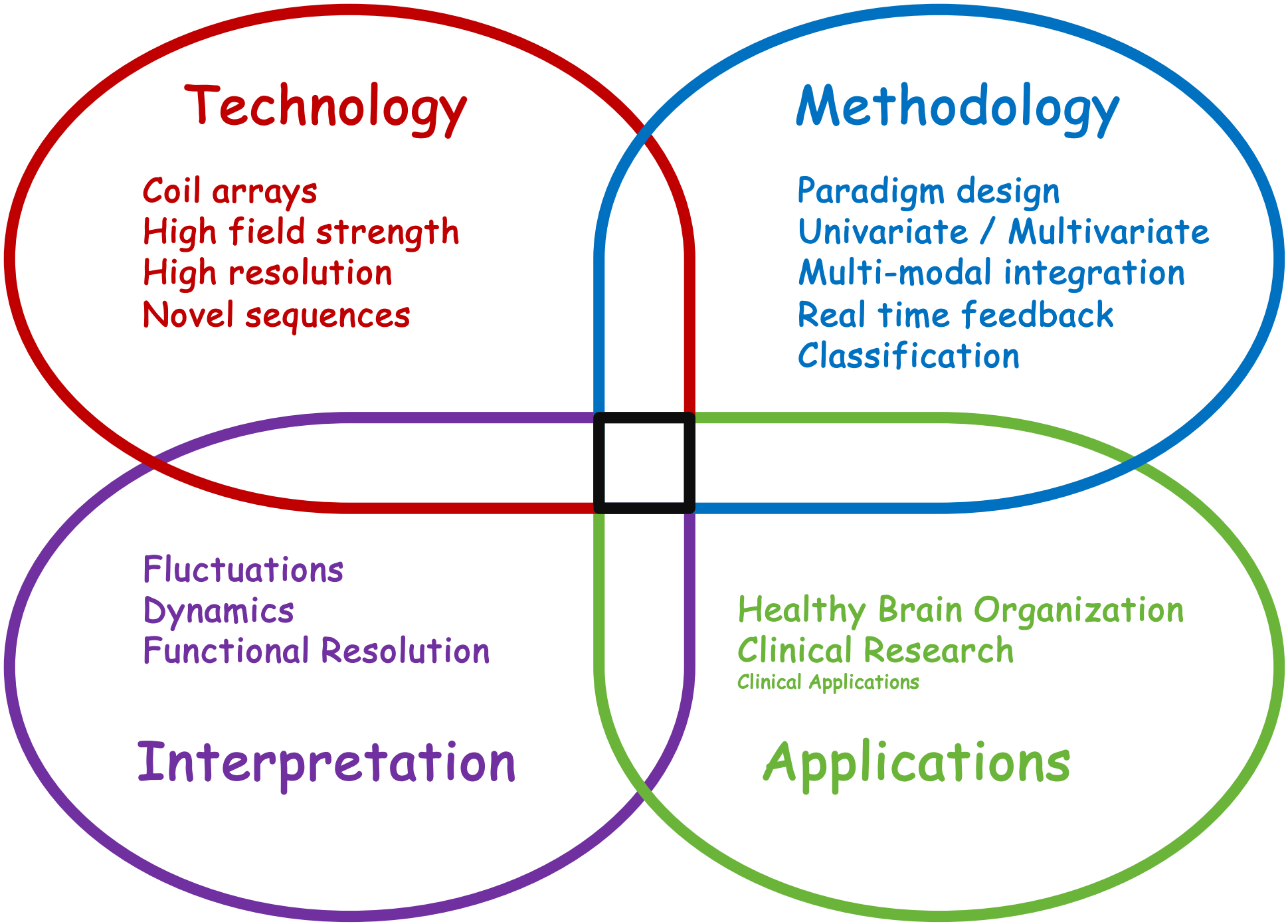
Five Key Factors For The Emergence of Functional MRI

1. **Magnetic properties of red blood cells**
2. **Activation related hemodynamic changes**
3. **Spatial scale of brain activation**
4. **Echo Planar Imaging**
5. **Prevalence of MRI scanners**



Motor (black)
Primary Sensory (red)
Integrative Sensory (violet)
Basic Cognition (green)
High-Order Cognition (yellow)
Emotion (blue)

J. Illes, M. P. Kirschen, J. D. E. Gabrielli,
Nature Neuroscience, 6 (3)m p.205


Technology
Coil arrays
High field strength
High resolution
Novel sequences
Methodology
Paradigm design
Univariate / Multivariate
Multi-modal integration
Real time feedback
Classification
Fluctuations
Dynamics
Functional Resolution
Interpretation
Healthy Brain Organization
Clinical Research
Clinical Applications
Applications

Brief History of Brain Imaging

1. **Lesion-based Mapping.**
2. **Anatomic Imaging.**
3. **Hemodynamic and Metabolic Imaging.**
4. **Electrophysiologic Imaging**
5. **Functional MRI**

Parametric manipulation of brain activation demonstrated that BOLD contrast approximately followed the level of brain activation: visual system (Kwong et al., 1992), auditory system (Binder et al., 1994), and motor system (Rao et al., 1996).

The use of continuous variation of visual stimuli parameters as a function of time was proven a powerful method for fMRI-based retinotopy: (Engel et al., 1994, Deyoe et al., 1994, Sereno et al., 1995).

Event-related fMRI was first demonstrated (Blamire et al., 1992).

Application of event-related fMRI to cognitive activation was shown (Buckner et al., 1996, McCarthy et al., 1997).

Development of mixed event-related and block designs was put forward: (Donaldson et al., 2002).

Paradigms were demonstrated in which the activation timing of multiple brain systems timing was orthogonal, allowing multiple conditions to be cleanly extracted from a single run (Courtney et al., 1997).

High resolution maps were created: For spatial resolution: ocular dominance columns (Menon et al., 1997, Cheng et al., 2001) and cortical layer activation maps were created (Logothetis et al., 2002).

Extraction of information at high spatial frequencies within regions of activation was demonstrated (Haxby et al., 2001).

For temporal resolution: Timings from ms to hundreds of ms were extracted (Ogawa et al., 2000, Menon et al., 1998, Henson et al., 2002, Bellgowan et al., 2003).

The development of "deconvolution" methods allowed for rapid presentation of stimuli (Dale and Buckner, 1997).

Early BOLD contrast models were put forward: (Ogawa et al., 1993, Buxton and Frank, 1997).

More sophisticated models were published that more fully integrated the latest data on hemodynamic and metabolic changes (Buxton et al., 2004).

The development of "clustered volume" acquisition was put forth as a method to avoid scanner noise artifacts: (Edmister et al., 1999).

The findings of functionally related resting state correlations: (Biswal et al., 1995) and regions that consistently show deactivation (Binder et al., 1999, Raichle et al., 2001) were described.

Observation of the pre-undershoot in fMRI (Hennig et al., 1997, Menon et al., 1995, Hu et al., 1997) and correlation with optical imaging was reported (Malonek and Grinvald, 1996).

Simultaneous use of fMRI and direct electrophysiological recording in non-human primate brain during visual stimulation elucidated the relationship between fMRI and BOLD contrast. (Logothetis et al., 2001). Simultaneous electrophysiological recordings in animal models revealed a correlation between negative signal changes and decreased neuronal activity (Shmuel et al., 2002). Simultaneous electrophysiological recordings in animal models provided evidence that inhibitory input could cause an increase in cerebral blood flow (Matheiesen et al., 1998).