Lecture Dav	Date	Room	Time	Торіс	Lecturer	e-mail
1 Friday	6/5/15	5 Bldg 40, Rm 1201/3	2:00 PM	Introduction to Course & A history of fMRI	Peter Bandettini	bandettini@nih.gov
2 Monday	6/8/15	5 Bldg 49, Rm 1A51/9	2:00 PM	fMRI & MRI at the NIH today - an overview of the current research	Sean Marrett	marretts@mail.nih.gov
3 Wednesday	6/10/15	5 Bldg 40, Rm 1201/3	2:00 PM	AFNI plus SUMA: viewing your data	Bob Cox	robertcox@mail.nih.gov
4 Friday	6/12/15	5 Bldg 40, Rm 1201/3	2:00 PM	AFNI plus SUMA: analyzing your data	Bob Cox	robertcox@mail.nih.gov
5 Monday	6/15/15	5 Bldg 40, Rm 1201/3	2:00 PM	Stoked! Surfing Functional and Anatomical Connectivity Like Never Before	Ziad Saad	saadz@mail.nih.gov
6 Wednesday	6/17/15	5 Bldg 40, Rm 1201/3	2:00 PM	Basics of MRI - and basic safety in MRI	Vinai Roopchansingh	roopchansinghv@mail.nih.gov
7 Friday	6/19/15	5 Bldg 40, Rm 1201/3	2:00 PM	Artifacts in MRI and how to identify them	Vinai Roopchansingh	roopchansinghv@mail.nih.gov
8 Monday	6/22/15	5 Bldg 40, Rm 1201/3	2:00 PM	Advanced MRI and fMRI Acquisition Methods	Souheil Inati	souheil.inati@nih.gov
9 Wednesday	6/24/15	5 Bldg 40, Rm 1201/3	2:00 PM	fMRI: What can and cannot be done?	Bob Cox	robertcox@mail.nih.gov
10 Friday	6/26/15	5 Bldg 40, Rm 1201/3	2:00 PM	Functional MRI contrast and the limits of spatial and temporal resolution	Peter Bandettini	bandettini@nih.gov
11 Monday	6/29/15	5 Bldg 40, Rm 1201/3	2:00 PM	fMRI Paradigm Designs and Processing Methods	Peter Bandettini	bandettini@nih.gov
12 Wednesday	7/1/15	5 Bldg 40, Rm 1201/3	2:00 PM	fMRI methods that never quite caught on	Peter Bandettini	bandettini@nih.gov
13 Monday	7/6/15	5 Bldg 40, Rm 1201/3	2:00 PM	Basic tradeoffs/constraints in fMRI methodology and applications	Jen Evans	jennifer.evans@nih.gov
14 Wednesday	7/8/15	5 Bldg 40, Rm 1201/3	2:00 PM	Perfusion MRI	Lalith Talagala	talagalal@mail.nih.gov
15 Friday	7/10/15	5 Bldg 40, Rm 1201/3	2:00 PM	Statistics of fMRI	Gang Chen	gangchen@mail.nih.gov
16 Monday	7/13/15	5 Bldg 40, Rm 1201/3	2:00 PM	How do we know what signal is neural and what is not?	Dan Handwerker	handwerkerd@mail.nih.gov
17 Wednesday	7/15/15	5 Bldg 35A, Rm 640	2:00 PM	Multi-modal imaging, EEG-fMRI	Silvina Horovitz	silvina.horovitz@nih.gov
18 Friday	7/17/15	5 Bldg 40, Rm 1201/3	2:00 PM	Computational Modeling of fMRI	Biyu He	biyu.he@nih.gov
19 Monday	7/20/15	5 Bldg 40, Rm 1201/3	2:00 PM	fMRI Mediation analysis for fMRI based pain assessment	Lauren Atlas	lauren.atlas@nih.gov
20 Wednesday	7/22/15	5 Bldg 40, Rm 1201/3	2:00 PM	Approaches to functional activity mapping during natural viewing	Brian Russ	russbe@mail.nih.gov
21 Friday	7/24/15	5 Bldg 40, Rm 1201/3	2:00 PM	Studying CNS diseases with advanced MRI	Pascal Sati	pascal.sati@nih.gov
22 Monday	7/27/15	5 Bldg 40, Rm 1201/3	2:00 PM	Quantitative MRI	Govind Bhagavatheeshwaran	govind.bhagavatheeshwaran@nih.gov
23 Wednesday	7/29/15	5 Bldg 40, Rm 1201/3	2:00 PM	Measuring structural brain change over time	Adam Thomas	adamt@nih.gov
24 Friday	7/31/15	5 Bldg 40, Rm 1201/3	2:00 PM	Brain Reading with fMRI	Chris Baker	bakerchris@mail.nih.gov
25 Monday	8/3/15	5 Bldg 40, Rm 1201/3	2:00 PM	Anatomical and Functional Neuroimaging in Animal Models	Afonso Silva	SilvaA@ninds.nih.gov
26 Wednesday	8/5/15	5 Bldg 40, Rm 1201/3	2:00 PM	fMRI Data Sharing	Dan Handwerker	handwerkerd@mail.nih.gov
27 Friday	8/7/15	5 Bldg 49, Rm 1A51/9	2:00 PM	fMRI of Mood Disorders	Allison Nugent	nugenta@gmail.com
28 Monday	8/10/15	5 Bldg 40, Rm 1201/3	2:00 PM	Resting State fMRI	Catie Chang	catie.chang@nih.gov
29 Wednesday	8/12/15	5 Bldg 40, Rm 1201/3	2:00 PM	Dynamic Resting State fMRI assessment	Javier Gonzalez-Castillo	javier.gonzalez-castillo@nih.gov
30 Friday	8/14/15	5 Bldg 40, Rm 1201/3	2:00 PM	Approaches to dealing with motion in resting state fMRI	Jonathan Power	jonathan.power@nih.gov
31 Monday	8/17/15	5 Bldg 40, Rm 1201/3	2:00 PM	Multi-echo EPI for resting state and activation based fMRI	Javier Gonzalez-Castillo	javier.gonzalez-castillo@nih.gov
32 Wednesday	8/19/15	5 Bldg 40, Rm 1201/3	2:00 PM	Methods for whole-brain comparisons of resting state connectivity	Steve Gotts	gottss@mail.nih.gov
33 Friday	8/21/15	5 Bldg 40, Rm 1201/3	2:00 PM	Prospective motion correction - is it better?	Andy Derbyshire	john.derbyshire@nih.gov
34 Monday	8/24/15	5 Bldg 40, Rm 1201/3	2:00 PM	T1 Contrast, MPRAGE and MT	Peter van Gelderen	pg24y@nih.gov
35 Wednesday	8/26/15	5 Bldg 40, Rm 1201/3	2:00 PM	fMRI and Development	Danny Pine	pined@mail.nih.gov
36 Friday	8/28/15	5 Bldg 40, Rm 1201/3	2:00 PM	Diffusion MRI	Joelle Sarlis	sarllsjo@mail.nih.gov
37 Monday	8/31/15	5 Bldg 40, Rm 1201/3	2:00 PM	What you can and can't do with diffusion MRI	Carlo Pierpaoli	cp1a@nih.gov
38 Wednesday	9/2/15	Bldg 40, Rm 1201/3	2:00 PM	Contentious Issues in fMRI	Peter Bandettini	bandettini@nih.gov
39 Friday	9/4/15	5 Bldg 49, Rm 1A51/9	2:00 PM	Is the Future of fMRI in the assessment of the individual?	Peter Bandettini	bandettini@nih.gov

## **A Brief History of 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



ISSN 1053-8119 Volume 62, Issue 2, August 15, 2012



# NeuroImage

*Editor-in-Chief* Peter Bandettini



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

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SciVerse ScienceDirect



	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
Jac	k 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	
	5	Finding the BOLD effect in brain images	Seiji Ogawa	
The first BOLD Brain Activation Results	6	Record of a single fMRI experiment in May of 1991	Ken Kwong	
	7	Development of functional Imaging in the human brain (fMRI); the university of Minnesota experience	Kamil Ugurbil	
	8	Sewer pipe, epoxy, wire, and finger tapping: the start of fMRI at the Medical College of Wisconsin	Peter Bandettini	
	9	The NIH experience in first advancing fMRI	Robert Turner	
	10	The Yale Experience in first advancing fMRI	Andrew Blamire	
Developments in Pulse Sequences, Imaging Methods, and Hardware for fMRI	11	How the challenges of auditory fMRI led to general advancements for the field	Tom Talavage	
	12	Correction of geometric distortion in fMRI data	Peter Jezzard	
	13	Echo Planar Imaging before and after fMRI: a personal history	Mark Cohen & Franz Schmitt	
	14	Local Head Gradient Coils: wondow(s) of opportunity	Eric Wong	
	15	Multi-echo acquisition	Stefan Posse	

	16	Perfusion MRI Imaging: evolution from initial developments to functional studies	Seong-Gi Kim
	17	The PRESTO technique for fMRI	Peter van Gelderen
	18	Real Time fMRI and its application to neurofeedback	Nikolaus Weiskopf
	19	Functional spectroscopy to no- gradient fMRI	Jurgen Hennig
	20	Ultrafast Inverse imaging techniques for fMRI	Fa-Hsuan Lin
	21	Spiral Imaging in fMRI	Gary Glover
	22	fMRI using steady-state free precession (SSFP) sequences	Karla Miller
	23	The rapid development of high speed, resolution, and precision in fMRI	David Feinberg & Essa Yacoub
	24	The road to functional imaging at ultrahigh fields	Kamil Ugurbil
	25	A review of the development of vascular space occupancy (VASO) fMRI	Hanzhang Lu
The emergence of processing and display packages	26	AFNI: what a long strange trips its been	Bob Cox
	27	Brain Voyager - past, present, and future	Rainer Goebel
	28	Cortical Cartography and Caret software	David van Essen
	29	FIASCO, STIMULATE, VoxBo, MEDx, Early fMRI Software: Where are they now?	Geoff Aguirre
	30	SUMA	Ziad Saad
	31	Free Surfer	Bruce Fischl
	32	FSL	Mark Jenkinson
	33	SPM: a history	John Ashburner
Development of Processing Methods for fMRI	34	Bayesian Inference in fMRI	Mark Woolrich

	35	Multiple testing corrections, nonparametric methods, and Random Field Theory	Tom Nichols
	36	A review and synthesis of the first 20 years of PET and fMRI studies of spoken language and reading	Cathy Price
	37	Cross-correlation: an fMRI signal- processing strategy	Jim Hyde & Andrzej Jesmanowicz
	38	Multivariate patterns analysis of fMRI: the early beginnings	Jim Haxby
	39	A short history of causal modeling of fMRI data	Klaas Enno Stephan & Alard Roebroeck
	40	The role of physiologic noise in resting-state functional connectivity	Rasmus Birn
	41	General Linear Model and fMRI: does love last forever?	Jean-Babtiste Poline
	42	From simple graphs to the connectome: networks in neuroimaging	Olaf Sporns
	43	Tracing the route to path analysis in neuroimaging	Randy McIntosh
	44	Modeling with independent components	Christian Beckmann
	45	A brief history of resting state: the Washington university perspective	Avi Snyder & Marcus Raichle
	46	Brain templates and atlases	Alan Evans
Methodological Developments, Issues, and Mechanisms	47	The role of susceptibility weighted imaging in functional MRI	Mark Haacke & Yongquan Ye
	48	Calibrated fMRI	Rick Hoge
	49	Resting state fMRI: a personal history	Bharat Biswal
	50	Voodoo and circularity errors	Ed Vul
	51	Diffusion modulation of the fMRI signal	Alan Song
	52	Dynamic Models of BOLD contrast	Rick Buxton
	53	Intracortical Recordings and fMRI: An attempt to study operational modules and networks	Nikos Logothetis

	simultaneously.	
54	The Great Brain versus Vein Debate	Ravi Menon
55	Linear systems analysis of the fMRI signal	Geoff Boynton
56	Quantitative fMRI and oxidative neuroenergetics	Fahmeed Hyder & Douglas Rothman
57	The meaning of fMRI signals	Arno Villringer
58	IRON fMRI measurements of CBV and implications for BOLD signal	Joe Mandeville
59	Using manganese-enhanced MRI to understand BOLD	Afonso Silva
60	The characterization of dynamic susceptibility effects	Robert Weisskoff
61	The continuing challenge of understanding and modeling hemodynamic variation in fMRI	Dan Handwerker
62	Ultra-high resolution fMRI at ultra- high field	Noam Harel
63	Revealing Ocular Dominance Columns using high resolution functional MRI	Kang Cheng
64	Inflow effects on functional MRI	Jia Hong Gao
 65	Neuronal inhibition and excitation, and the dichotomic control of brain hemodynamic and oxygen responses	Martin Lauritzen
66	The history and role of long duration stimulation in fMRI	Gunnar Krueger
67	A personalized history of EEG-fMRI integration	Helmut Laufs
68	Mental Chronometry with MRI	Ravi Menon
69	Pharmacologic Magnetic Resonance Imaging (phMRI): Imaging Drug Action in the Brain.	Bruce Jenkins
70	Task induced deactivation and the "resting" state	Jeff Binder

	71	The BOLD post-stimulus undershoot, one of the most debated issues in	Peter van Zijl	The Future	88	Is there a path beyond BOLD? Molecular Imaging of Brain Function	Alan Koretsky
		fMRI					
	72	The story of the initial dip in fMRI	Xiaoping Hu		89	The future of fMRI in Cognitive Neuroscience	Russ Poldrack
	73	Spin-echo fMRI: the poor relation?	David Norris		90	The future of acquisition speed,	Larry Wald
	74	Test-retest reliability in fMRI: or How	David McGonigle			coverage, sensitivity, and resolution	
		I learned to stop worrying and love the variability		_	91	The history of the future of the Bayesian Brain	Karl Friston
	75	Which "neural activity" do you	Chris Singh				
		mean? fMRI, MEG, oscillations and			92	Quantitative functional MRI:	Bruce Pike
		neurotransmitters	<b>D</b>	4		concepts, issues, and future	
	/6	Diffusion, Confusion and functional	Denis LeBihan			challenges	
					93	The future of ultra-high field MRI and fMRI for study of the human brain	Jeff Duyn
	77	The serendipitous discovery of the	Randy Buckner		94	Seeing patterns through the	Niko Kriegeskorte &
New Paradiam Designs	70	brain's default network	Mark Louis			hemodynamic veil - the future of	Elia Formisano
New Paradigin Designs	/0	a viable paradigm design	Wark Lowe		05	The future of fMPL connectivity	Stove Smith
	79	Event-related fMRL in Cognition	Scott Huettel	-	35	The future of fiviki connectivity	Steve Smith
	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Event related with in cognition	Scott nuctuer				
	80	The development of event-related fMRI designs	Tom Liu		96	The future of fMRI in clinical medicine	Ed Bullmore
	81	Targeting the functional properties	Rafi Malach		97	Future trends in Neuroimaging:	Uri Hasson
		of cortical neurons using fMR-				neuronaprocesses as expressed	
		adaptation				within real-life social contexts	
	82	Studying the freely-behaving brain with fMRI	Elanor Maguire		98	The future of fMRI with perfusion imaging	Geott Aguirre
	83	The mixed blocked and event-related	Joseph Dubis &				
		design	Steven Petersen	-	99	The future of fMRI and genetics	Andreas Meyer-
	84	Development of orthogonal task	Susan Courtney			research	Lindenberg
		cognition: the NIMH experience			100	The future of functionally related structural change assessment	Heidi Johansen- Berg
	85	A history of randomized task designs	Vince Clark		101	The future of the human	David van Essen &
					102	connectome	Kamii Ugurbii
	86	The development and use of phase	Steve Engel	-	102	for assessment of anatomy and	Jurgen Keichenbach
	00	encoded functional MRI designs	Steve Engel			function	
Education	87	The Evolution and current challenges	Bob Savoy		103	fMRI at 20: Has it changed the	Bruce Rosen
		in the teaching of functional MRI and				world?	
		functional brain imaging					

### 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.

#### angiography



#### **Gadolinium perfusion**

Diffusion







metabolic imaging (NAA)

#### magnetization transfer









### **IVIM: Intravoxel Incoherent Motion**

Denis Le Bihan, MD, PhD • Eric Breton, MS • Denis Lallemand, MD • Marie-Louise Aubin, MD • Jacqueline Vignaud, MD • Maurice Laval-Jeantet, MD

Radiology 1988; 168:497-505

## Separation of Diffusion and Perfusion in Intravoxel Incoherent Motion MR Imaging<sup>1</sup>



Robert Turner, PhD • Denis Le Bihan, MD, PhD • Joseph Maier, MS (EEE) • Robert Vavrek, MS (EEE) • L. Kyle Hedges, PhD • James Pekar, PhD

## Echo-Planar Imaging of Intravoxel Incoherent Motion<sup>1</sup> Radiology 1990; 177:407-414



Gradient factor b (s/mm2)

How it all came together...

## Five Key Factors For The Emergence of Functional MRI

- I. 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

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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.

210

#### CHEMISTRY: PAULING AND CORYELL PROC. N. A. S.

#### 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.<sup>1</sup>

Continuing our investigations of the magnetic properties and structure of hemoglobin and related substances,<sup>2</sup> 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.



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)

#### **Blood R2 proportional to Oxygenation**



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

١

2



...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 ecke pulse sequence with a spatial resolution of  $65 \times 65$ -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.  $\oplus$  1990 Academic Peres Inc.



## in vivo



### in vitro

#### 100% oxygenated blood





**20% O**<sub>2</sub>

**100% O**<sub>2</sub>

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<sub>0</sub>.



## Magnetic Resonance in Medicine "30 papers that shaped the field."





## 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. © 1991 Academic Press, Inc.





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

- I. Magnetic properties of red blood cells
- 2. Activation related hemodynamic changes
- 3. Spatial scale of brain activation
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- 5. Prevalence of MRI scanners

## The First Functional MRI Results (MGH)

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



## The First Functional MRI Results (MGH)

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



## 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 <u>Harvard</u> 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 <u>M.R.I.</u> scanner that took split-second images, faster than was usual at the time. This would become a standard technique for assessing blood perfusion in



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

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.



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\*<sup>†‡</sup> AND MARCUS E. RAICHLE\*<sup>†</sup>

\*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<sub>2</sub> was much smaller (5% of mean, nine subjects, three trials ner subject) and failed to attain sig.

nificance. This physiological uncoupling of CBF and CMRo<sub>2</sub> flow produced a highly significant decrease in the local OEF (-19% of mean), indicating that tissue Po<sub>2</sub> (and probably pH) rose during stimulation.

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.



The video that started it all. Aug 12, 1991: Tom Brady Plenary Lecture at SMRM, San Francisco





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.



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ght sti. 5in Gp 10 cm. slice cardene TR: 2:55 To=4\$ MAY9,91 **GE (BOLD) Contrast** IR 40 m Cel 3,50 - gestim. pre 3-30 (2P) gestim. pro 33-70 (38) 3 70 per phin GT-stim. dat disday -2 30 Pre. 40 post gent gepre. ang gent: gepre. ang gent: 7106 pstim. 25 yR IR 370 (0 V TI=1.05 S. 3.0 FR disday TR=35 TI=1100ms TE=42 40 per 40 post = 2 80 **IR (CBF) Contrast** 20 N 80 light of 30 maps ilstippe 3-30 (28) go per 40 40) pro 33-68 (49) irst. 67-80 (47) Tristin. sub looks good. only 270 charge. 20 rstim 74 (75) 4-30 33-65 67-80 The original block design irstim. sub (73) (subtraction 4) irstim. pre 235-8 13 14 16 18 19 25-21 rewing (16 together) 2-5 7 10-17 19-50 itstim.s Sn:lles (rit: n. pro 34-3840-47 49-65 67-80 Avg thim, (with seven x510) (44 together) purt (20) pre (25) instim. sub (45-> get mirstim. aug (save them)




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.





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**

ERIC C. WONG,\* A. JESMANOWICZ, AND JAMES S. HYDE

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





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







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.









Trying to figure out the basic mechanism.





## 



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. MAGNETIC RESONANCE IN MEDICINE 23, 37-45 (1992)



#### Perfusion Imaging

#### JOHN A. DETRE, \* † JOHN S. LEIGH, \* DONALD S. WILLIAMS, AND ALAN P. KORETSKY ‡ §

\* Metabolic Magnetic Resonance Research Center and Department of Biochemistry and Biophysics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104; and ‡Pittsburgh NMR Center for Biomedical Research and §Department of Biological Sciences, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213

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 <sup>1</sup>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 normocaphic rat brain under halothane anesthesia was determined to be  $105 \pm 16 \text{ cc} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$  (mean  $\pm \text{ SEM}$ , n = 3), in good agreement with values reported in the literature, and was sensitive to increases in arterial pCO<sub>2</sub>. This technique allows regional perfusion maps to be measured noninvasively, with the resolution of <sup>1</sup>H MRI, and should be readily applicable to human studies.  $\Rightarrow 1992$  Academic Pres, Inc.

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)

DONALD S. WILLIAMS\*, JOHN A. DETRE<sup>†‡</sup>, JOHN S. LEIGH<sup>†</sup>, AND ALAN P. KORETSKY<sup>\*§</sup>

\*Pittsburgh Nuclear Magnetic Resonance Center for Biomedical Research, and <sup>§</sup>Department of Biological Sciences, Carnegie Mellon University, Pittsburgh, PA 15213; and <sup>†</sup>Metabolic Magnetic Resonance Research Center, Department of Radiology, and <sup>‡</sup>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)  $T_{\text{lapp}}$  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·g<sup>-1</sup>·min<sup>-1</sup>. The injured region is dark due to low flow.

## Magnetic Resonance in Medicine "30 papers that shaped the field."



# Perfusion Contrast EPISTAR FAIR





## TI (ms) FAIR EPISTAR



- 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)

Society of Magnetic Resonance in Medicine Society for Magnetic Resonance Imaging

#### FUNCTIONAL MRI OF THE BRAIN

#### **Syllabus**

A Workshop Presented by the Society of Magnetic Resonance in Medicine and the Society for Magnetic Resonance Imaging

June 17-19, 1993 The Ritz-Carlton, Pentagon City Arlington, Virginia Denis Le Bihan National Institutes of Health Diagnostic Radiology Department Building 10, Room 1C-660 Bethesda, Maryland 20892

Robert Turner National Institutes of Health Laboratory of Cardiac Energetics Building 10, Room B1D-161 Bethesda, Maryland 20892

Michael E. Moseley Department of Radiology Stanford University Stanford, California 94305-5488

James S. Hyde Biophysics Research Institute Medical College of Wisconsin 8701 Waterton Plank Road Milwaukee, Wisconsin 53226

#### 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). The earliest successful magnetic resonance functional neuroimaging (MRFN) studies with BOLD contrast were made using a gradient-echo version of ecno-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



## NIH 4T



### Siemens' new 7T



## Five Key Factors For The Emergence of Functional MRI

- I. 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







#### **Visual Cortex Organization**



Right

Loft

Right

### **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

 $0.47 \times 0.47$  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



Yacoub et al. PNAS 2008
# 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

- I. 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



## **MRI vs. fMRI**

MRI

high resolution (1 mm)



one image

fMRI



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

#### Sir Peter Mansfield conceived of Echo Planar Imaging long before it was physically possible...

Spatial Mapping of the Chemical Shift in NMR, P. Mansfield. Magnetic Resonance in Medicine 1, 370-386 (1984).



#### LETTER TO THE EDITOR

#### A target field approach to optimal coil design

R Turner Department of Physics, Nottingham University, Nottingham NG7 2RD, UK

Received 2 May 1986

Abstract. Using a Fourier-Bessel expansion of the magnetic field generated by currents flowing on a cylinder, the relationship between current and field may be inverted. Hence the current density required to generate a specified target field  $B_z$  on the surface of a cylinder of smaller radius may be evaluated. Gradient, solenoidal and shim coil designs based on this approach provide exceptionally large usable volumes while remaining compact and, if necessary, of low inductance.



Figure 2. The arc configuration for a longitudinal gradient coil. The volume within which the gradient is uniform to 5% is shaded. Wire positions:

#### Snapshot Head Imaging at 0.5 T Using the Echo Planar Technique

#### R. J. ORDIDGE, R. COXON, A. HOWSEMAN, B. CHAPMAN, R. TURNER, M. STEHLING, AND P. MANSFIELD

Department of Physics, University of Nottingham, Nottingham NG7 2RD, United Kingdom

Received April 22, 1988; revised June 17, 1988

The echo planar imaging (EPI) method and related variants of this technique can produce complete two-dimensional images from the data collected in a single experiment lasting a fraction of a second. EPI methods are used at 0.5 T to produce snapshot images of the human head with a spatial resolution of less than 2 mm. © 1988 Academic Press, Inc.



FIG. 2. The gradient and RF pulse sequence used in the MBEST experiment. An unphased image is produced by taking the magnitude of the Fourier transformed data. The largest spin echoes occur midway through the experiment, thus providing discrimination against signal with a short  $T_2$  relaxation time.









### **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<sup>3</sup>
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<sup>3</sup> single shot EPI possible
2009 At 7T sub – mm single shot EPI for fMRI is possible

# Imaging System Components





# Five Key Factors For The Emergence of Functional MRI

- I. 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



"fMRI" or "functional MRI"

How it all came together...

# Five Key Factors For The Emergence of Functional MRI

- I. 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 (vellow 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

#### A bit more history...

- Event-Related fMRI (1993, 1996)
- Retinotopy (1995)
- Resting State fMRI (1995...2006)
- Ocular Dominance Columns (1997)
- High Field and Multi-channel Receive (2000)
- fMRI "Decoding" (2001)
- Intracortical recordings and fMRI (2001)
- DARPA Brain Reading Competition (2006)
- Approval for Pre-surgical Mapping (2007)



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. Proc. Natl. Acad. Sci. USA Vol. 93, pp. 14878–14883, December 1996 Neurobiology

# Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging

(neuroimaging/single trial/language/prefrontal)

### RANDY L. BUCKNER<sup>†‡§¶</sup>, PETER A. BANDETTINI<sup>†‡</sup>, KATHLEEN M. O'CRAVEN<sup>†||</sup>, ROBERT L. SAVOY<sup>†||</sup>, STEVEN E. PETERSEN<sup>\*\*††</sup>, MARCUS E. RAICHLE<sup>§\*\*††</sup>, AND BRUCE R. ROSEN<sup>†‡</sup>

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Contributed by Marcus E. Raichle, September 4, 1996









# fMRI of human visual cortex

Stephen A. Engel David E. Rumelhart Brian A. Wandell Department of Psychology, Adrian T. Lee Gary H. Glover Department of Radiology, Eduardo-Jose Chichilnisky Neuroscience Program, Michael N. Shadlen Department of Neurobiology, Stanford University, Stanford, California 94305, USA

NATURE · VOL 369 · 16 JUNE 1994



Proc. Natl. Acad. Sci. USA Vol. 93, pp. 2382–2386, March 1996 Neurobiology

# Mapping striate and extrastriate visual areas in human cerebral cortex

EDGAR A. DEYOE\*, GEORGE J. CARMAN<sup>†</sup>, PETER BANDETTINI<sup>‡</sup>, SETH GLICKMAN\*, JON WIESER\*, ROBERT COX<sup>§</sup>, DAVID MILLER<sup>¶</sup>, AND JAY NEITZ<sup>\*</sup>

\*Department of Cellular Biology and Anatomy, and Biophysics Research Institute, The Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226; <sup>†</sup>The Salk Institute for Biological Studies, La Jolla, CA 92037; <sup>‡</sup>Massachusetts General Hospital–NMR Center, Charlestown, MA 02129; <sup>§</sup>Biophysics Research Institute, The Medical College of Wisconsin, Milwaukee, WI 53226; and <sup>§</sup>Brown University, Providence, RI 02912

Communicated by Francis Crick, The Salk Institute for Biological Sciences, San Diego, CA, November 14, 1995 (received for review August 2, 1995)





#### **Resting State Correlations**





Activation: correlation with reference function seed voxel in motor cortex

Rest:

B. Biswal et al., MRM, 34:537 (1995)

# Activation-based fMRI and "resting state" f



Resting Correlation (Right Hand Seed)

300

400

500

60

#### Resting state fMRI: Why is this area important?

- The number of papers and applications has exploded.
- Neuronal, psychiatric, and developmental disorders may relate to altered connectivity.
- Methods are in their infancy, and rapidly evolving.
- Neuronal correlates of spontaneous fluctuations are not fully understood.



## Magnetic Resonance in Medicine "30 papers that shaped the field."



#### Distributed and Overlapping Representations of Faces and Objects in Ventral Temporal Cortex

James V. Haxby,<sup>1</sup>\* M. Ida Gobbini,<sup>1,2</sup> Maura L. Furey,<sup>1,2</sup> Alumit Ishai,<sup>1</sup> Jennifer L. Schouten,<sup>1</sup> Pietro Pietrini<sup>3</sup>

SCIENCE VOL 293 28 SEPTEMBER 2001



Logothetis et al. (2001) "Neurophysiological investigation of the basis of the fMRI signal" Nature, 412, 150-157



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).