Principles of Haemodynamic Coupling for fMRI

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Regulation of cerebral blood flow

- **Mosso (1881):** pulsation of brain increases with cognitive activity
- **Broca (1879):** increases in brain temperature with cerebral activity
- **Hill (1896):** no relationship between brain blood flow and activity
- **Fulton (1928):** increase in bruit from occipital AVM with visual attention
- **Kety (1960):** autoradiographic methods for regional blood flow quantitation
- **Lassen (1963):** in vivo tomographic assessment of regional blood flow

Regulation of cerebral blood flow

- **Mosso (1881):** pulsation of brain increases with cognitive activity
- **Broca (1879):** increases in brain temperature with cerebral activity
- **Roy and Sherrington (1890):** evidence for regulation of blood flow by local brain metabolism
- **Hill (1896):** no relationship between brain blood flow and activity
- **Fulton (1928):** increase in bruit from occipital AVM with visual attention
- **Kety (1960):** autoradiographic methods for regional blood flow quantitation
- **Lassen (1963):** in vivo tomographic assessment of regional blood flow

ON THE REGULATION OF THE BLOOD-SUPPLY OF THE BRAIN.

By C. S. ROY, M.D., F.R.S., *Professor of Pathology, University of Cambridge,* AND C. S. SHERRINGTON, M.B., M.A., *Fellow of Gonville and Caius College. Lecturer on Physiology in the School of St Thomas's Hospital, London.*

Plates II., III. and IV.

From the Cambridge Pathological Laboratory.

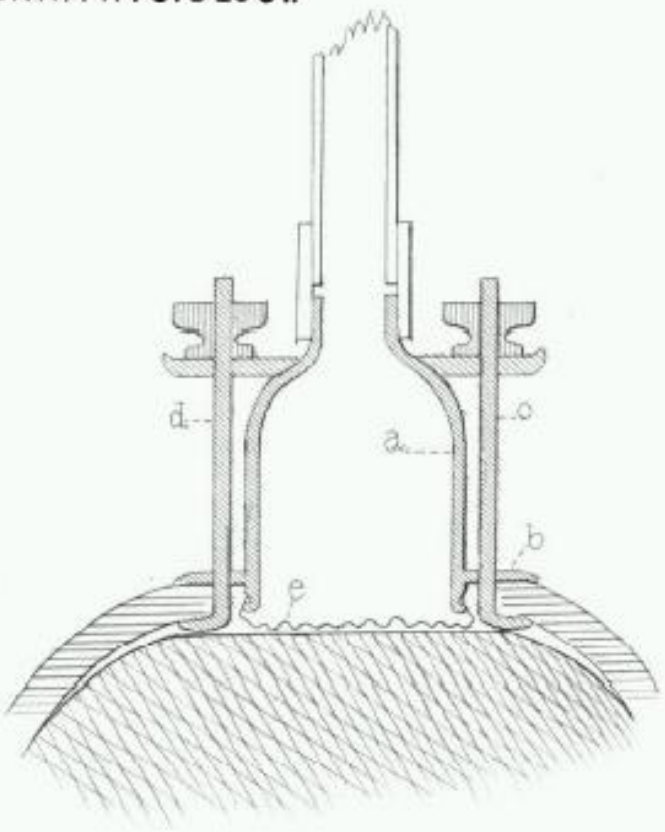


Fig. 1.

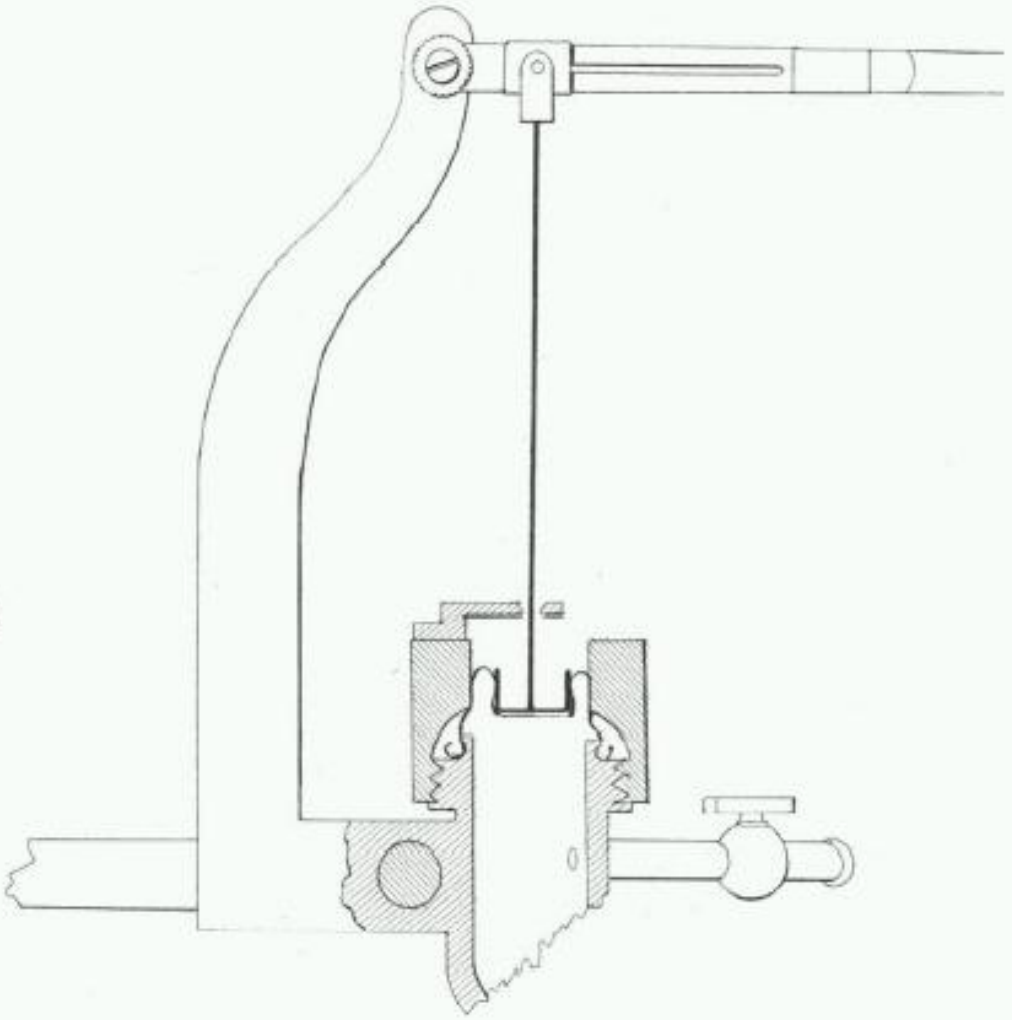


Fig 1a.

Cerebral blood flow follows systemic arterial pressure changes in the anesthetised dog

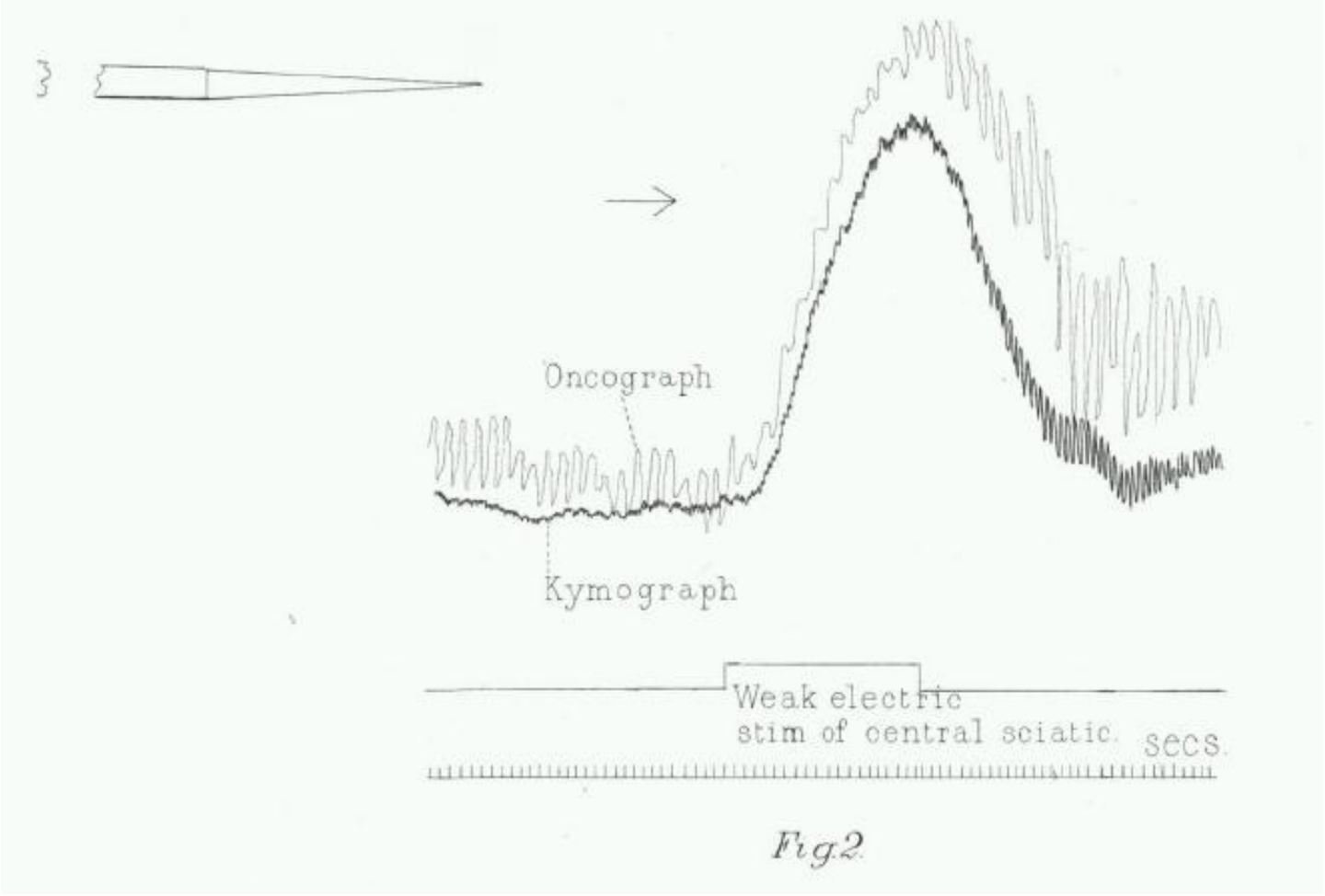
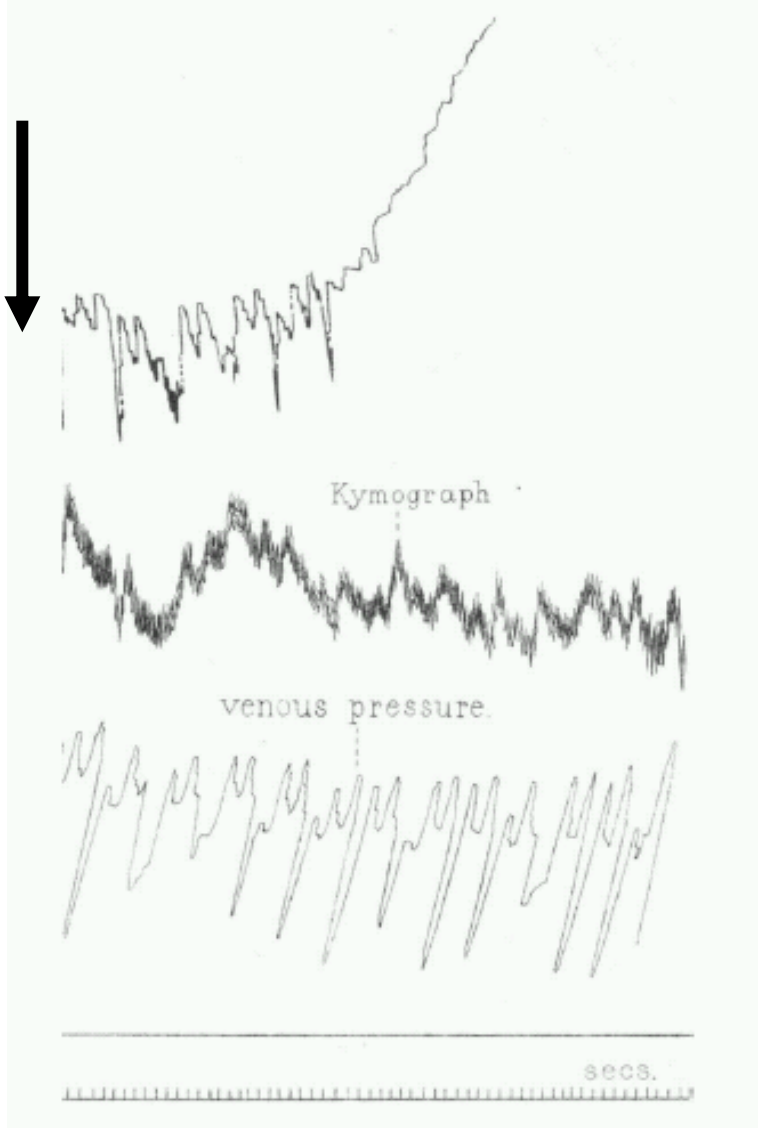


Fig 2.

Cerebral blood flow changes indepedently of arterial blood pressure with local infusion of acid or supernatent of brain extract

Infusion of supernatant of brain extract



Brain volume measure

Arterial blood pressure

Implications for brain function and in the clinic

A refinement to the concept: *reduction* in oxygen extraction fraction with brain activity

1: Science. 1988 Jul 22;241(4864):462-4.

Nonoxidative glucose consumption during focal physiologic neural activity.

Fox PT, **Raichle ME**, **Mintun MA**, **Dence C**.

Division of Radiation Sciences, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis 63110.

Brain glucose uptake, oxygen metabolism, and blood flow in humans were measured with positron emission tomography, and a resting-state molar ratio of oxygen to glucose consumption of 4.1:1 was obtained. Physiological neural activity, however, increased glucose uptake and blood flow much more (51 and 50 percent, respectively) than oxygen consumption (5 percent) and produced a molar ratio for the increases of 0.4:1. Transient increases in neural activity cause a tissue uptake of glucose in excess of that consumed by oxidative metabolism, acutely consume much less energy than previously believed, and regulate local blood flow for purposes other than oxidative metabolism.

PMID: 3260686 [PubMed - indexed for MEDLINE]

A century on (1992): the BOLD hypothesis

Neurovascular coupling and *Blood Oxygenation Level Dependent* functional imaging contrast

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 5675–5679, June 1992
Neurobiology

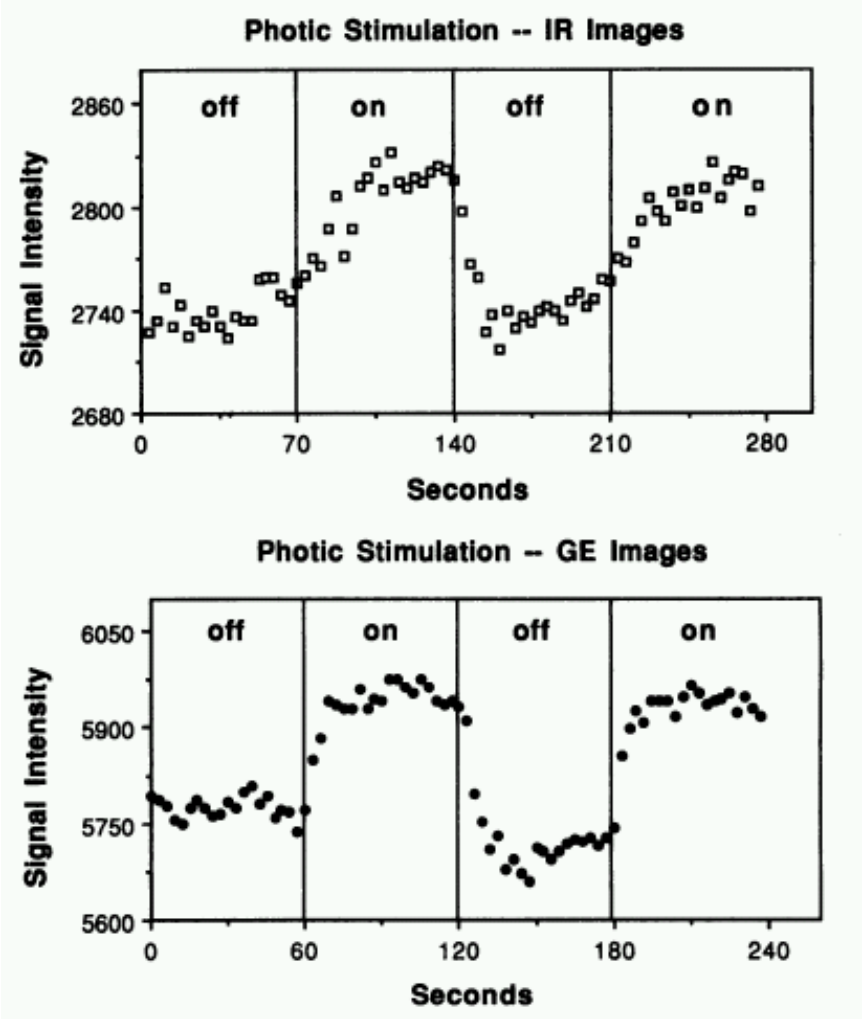
Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation

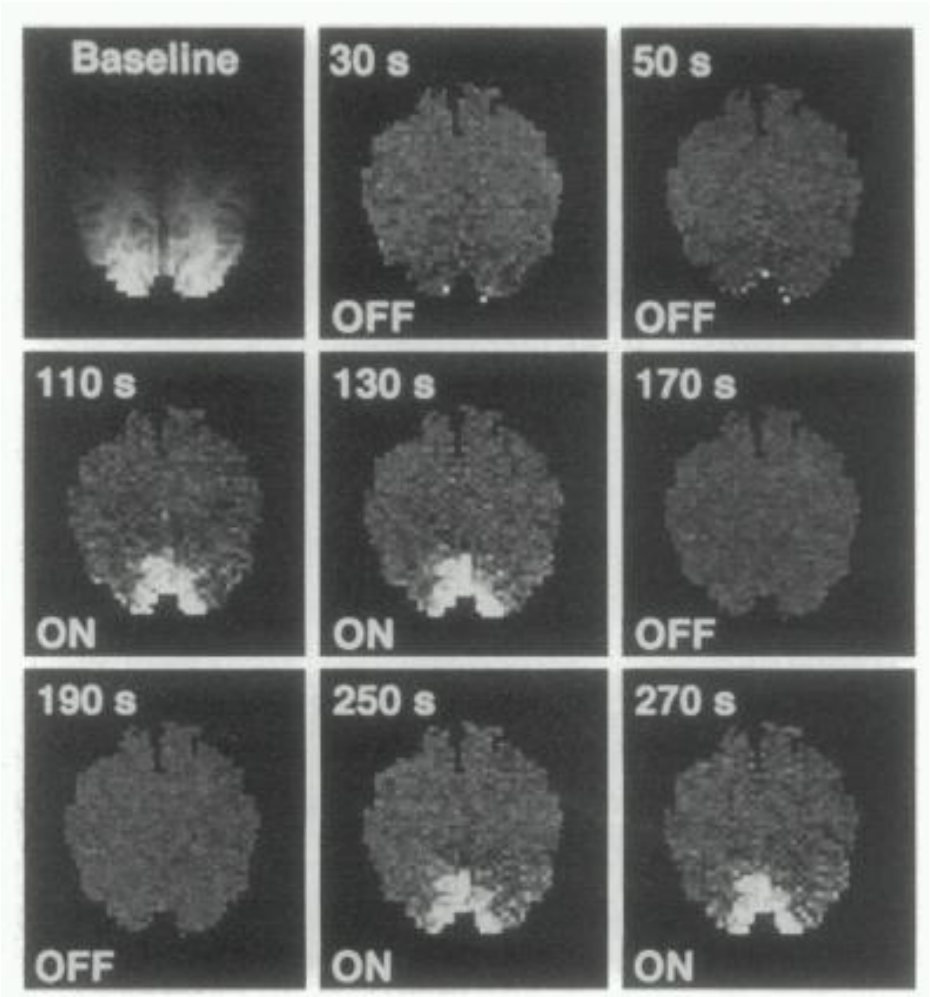
KENNETH K. KWONG†, JOHN W. BELLIVEAU†, DAVID A. CHESLER†, INNA E. GOLDBERG†, ROBERT M. WEISSKOFF†, BRIGITTE P. PONCELET†, DAVID N. KENNEDY†, BERNICE E. HOPPEL†, MARK S. COHEN†, ROBERT TURNER‡, HONG-MING CHENG§, THOMAS J. BRADY†, AND BRUCE R. ROSEN†

†MGH–NMR Center, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129; ‡National Institutes of Health, Laboratory of Cardiac Energetics, National Heart, Lung, and Blood Institute, Bethesda, MD 20892; and §Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston, MA 02114

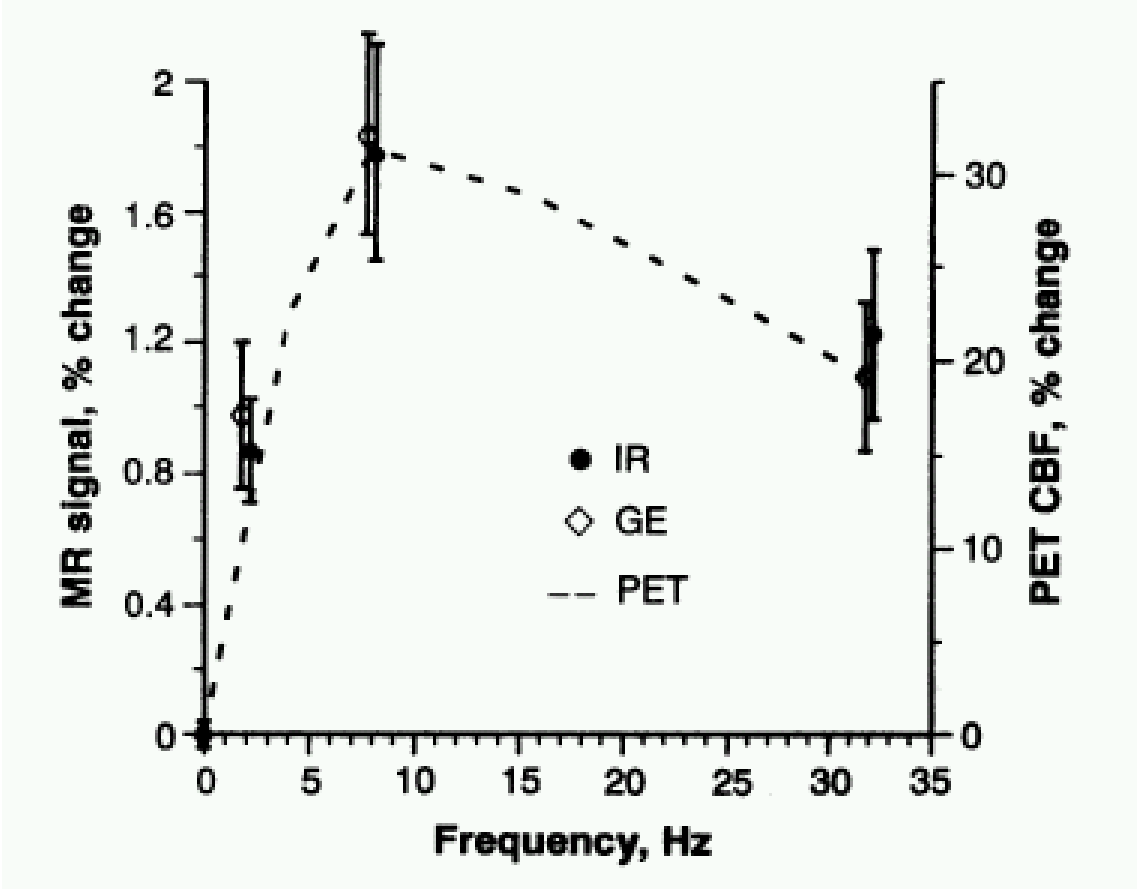
Communicated by David H. Hubel, March 26, 1992

The *decrease* in deoxyhemoglobin with brain activation is associated with local *increase* in gradient echo MRI signal



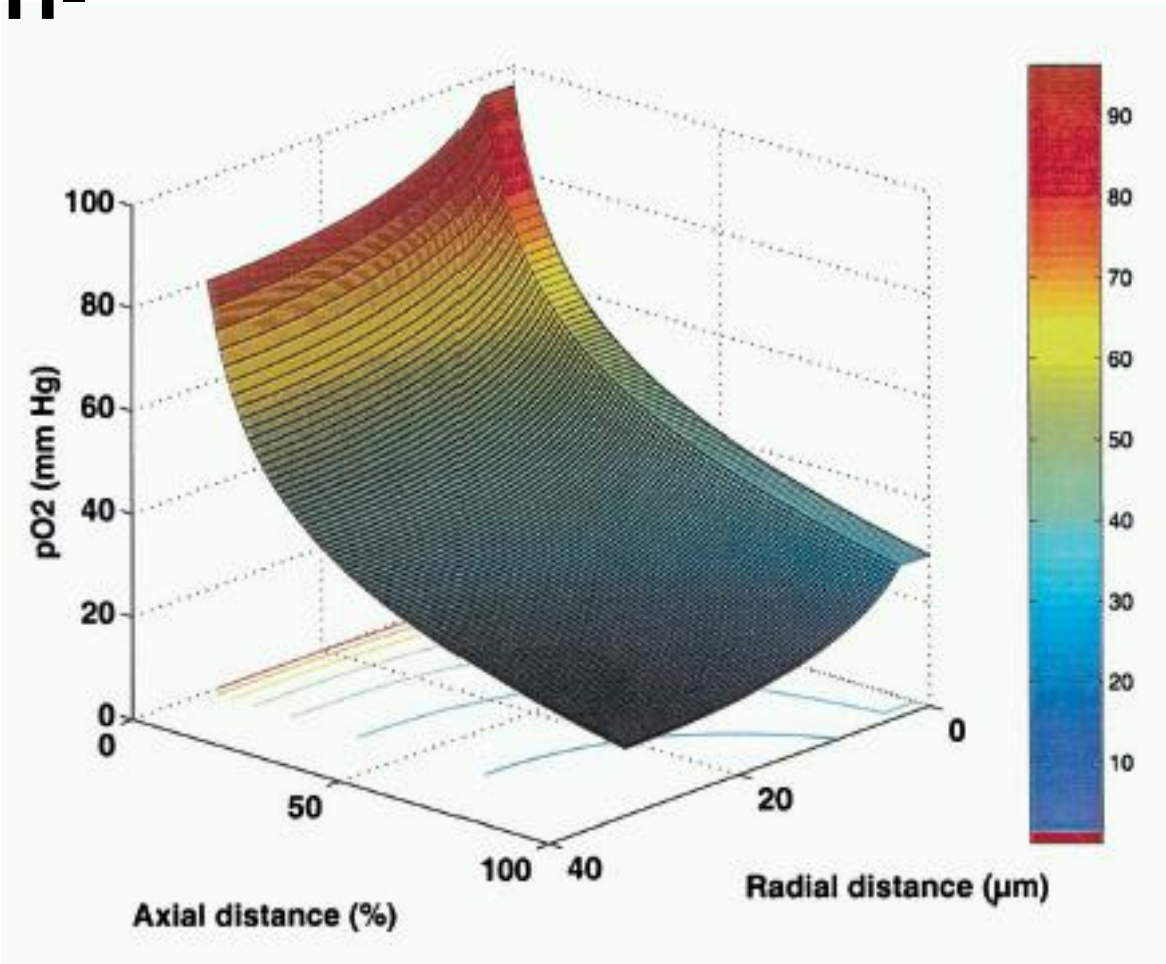


Stimulation of visual cortex shows frequency-dependent effects consistent with aggregate neuronal response and PET measures of local CBF



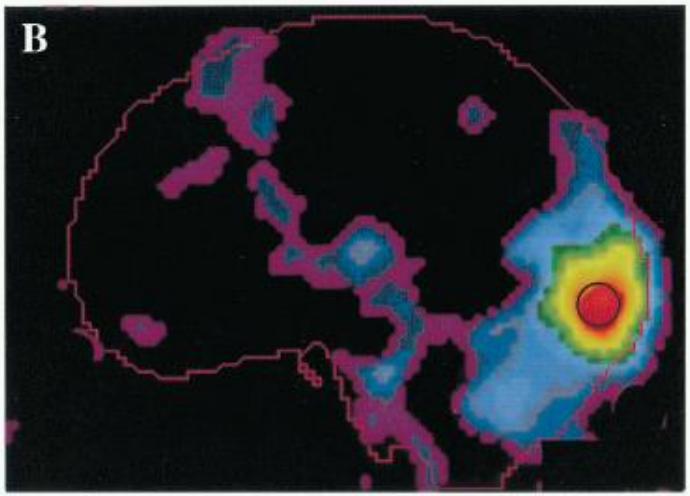
Are local CBF driven by local acidic metabolite release under conditions of normal physiology?

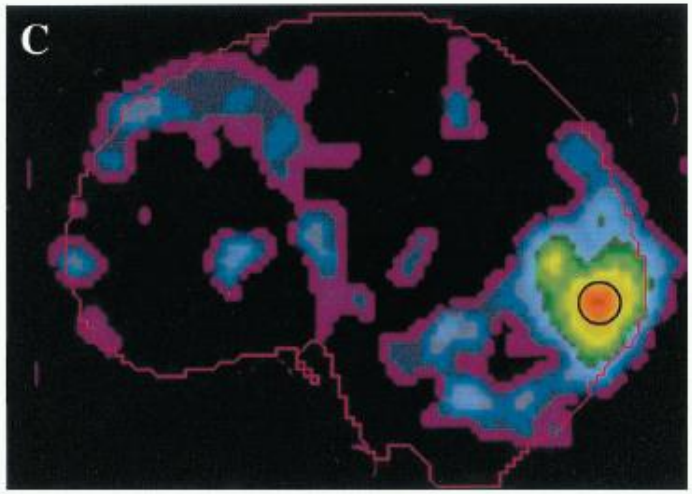
Modelling of peri-capillary PO_2

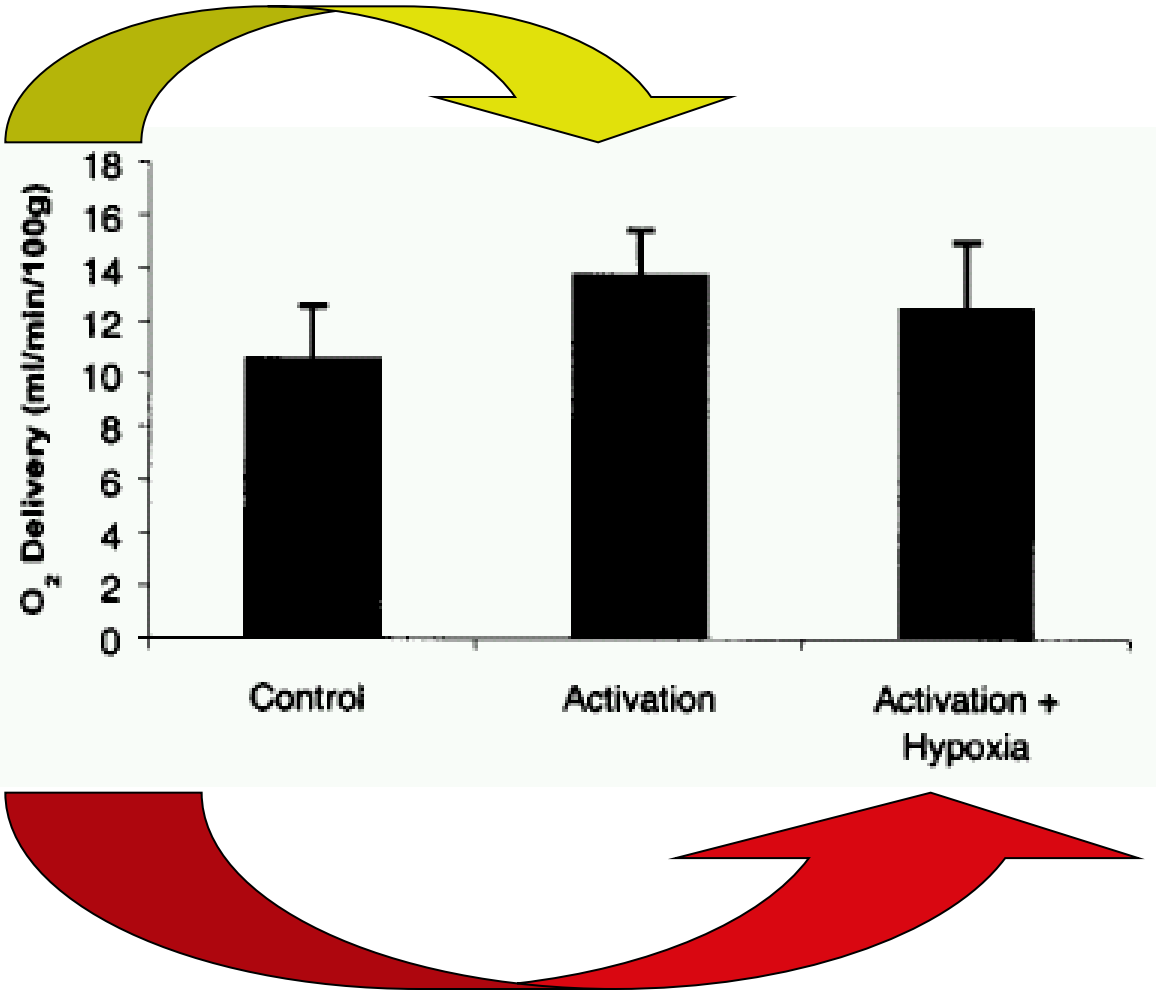


MA Mintun et al. PNAS 98 (2001) 6859

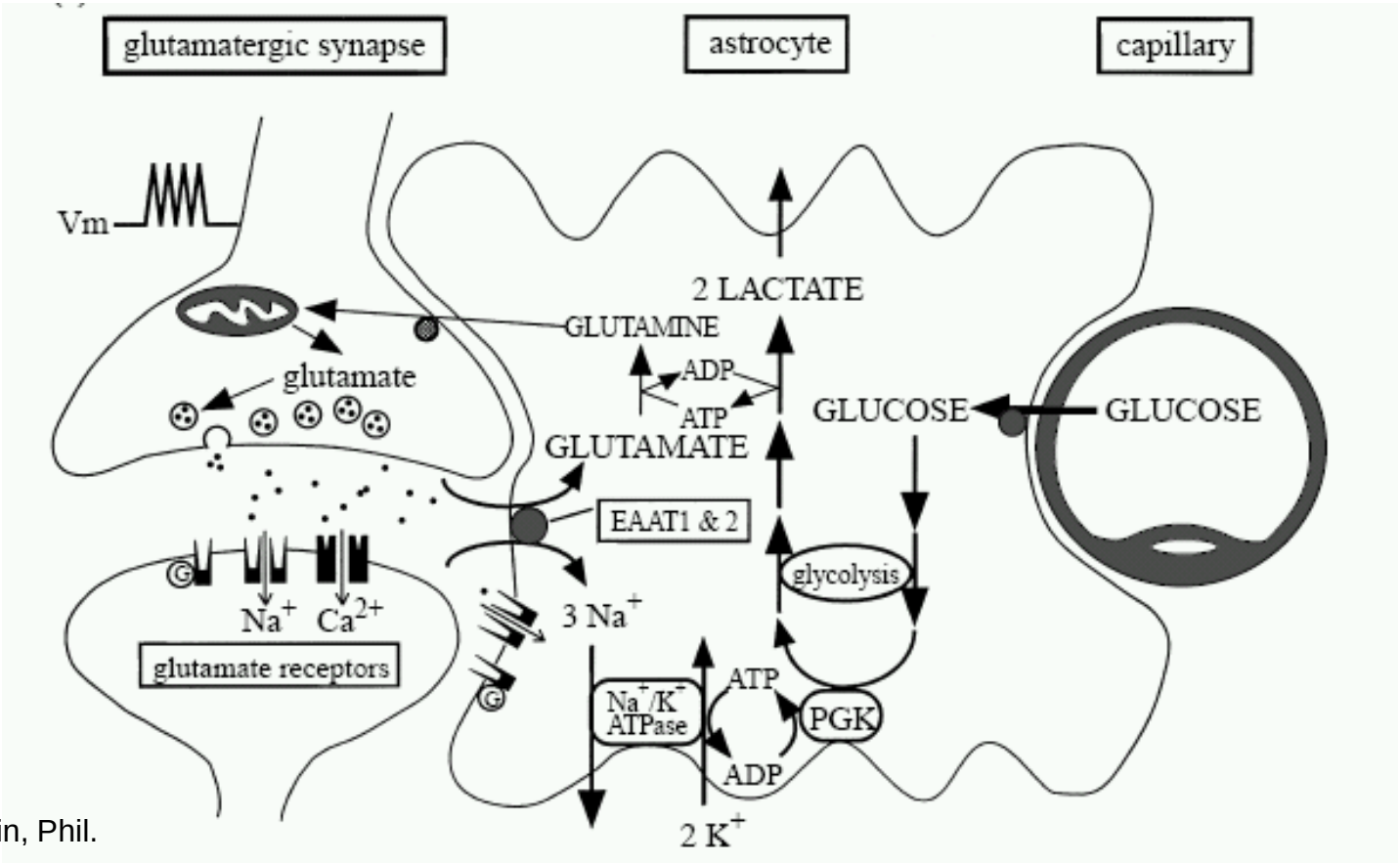
Moderate hypoxia does not increase the hyperaemic response to neuronal activation







Introducing the astrocyte as an intermediate in neurovascular coupling



Magistretti and Pellerin, Phil. Trans.R. Soc. 354 (1999)1155

Metabolic integration of a “neurovascular unit”

Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation

Micaela Zonta[1], María Cecilia Angulo[1,2], Sara Gobbo[1], Bernhard Rosengarten[3], Konstantin-A. Hossmann[3], Tullio Pozzan[1] and Giorgio Carmignoto[1]

[1] *Istituto CNR di Neuroscienze and Dipartimento di Scienze Biomediche Sperimentali, Università di Padova, viale G. Colombo 3, 35121 Padova, Italy*

[2] *Centro Internacional de Física, Ed. Manuel Ancízar, Ciudad Universitaria, Bogotá, Colombia*

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The first two authors contributed equally to this work.

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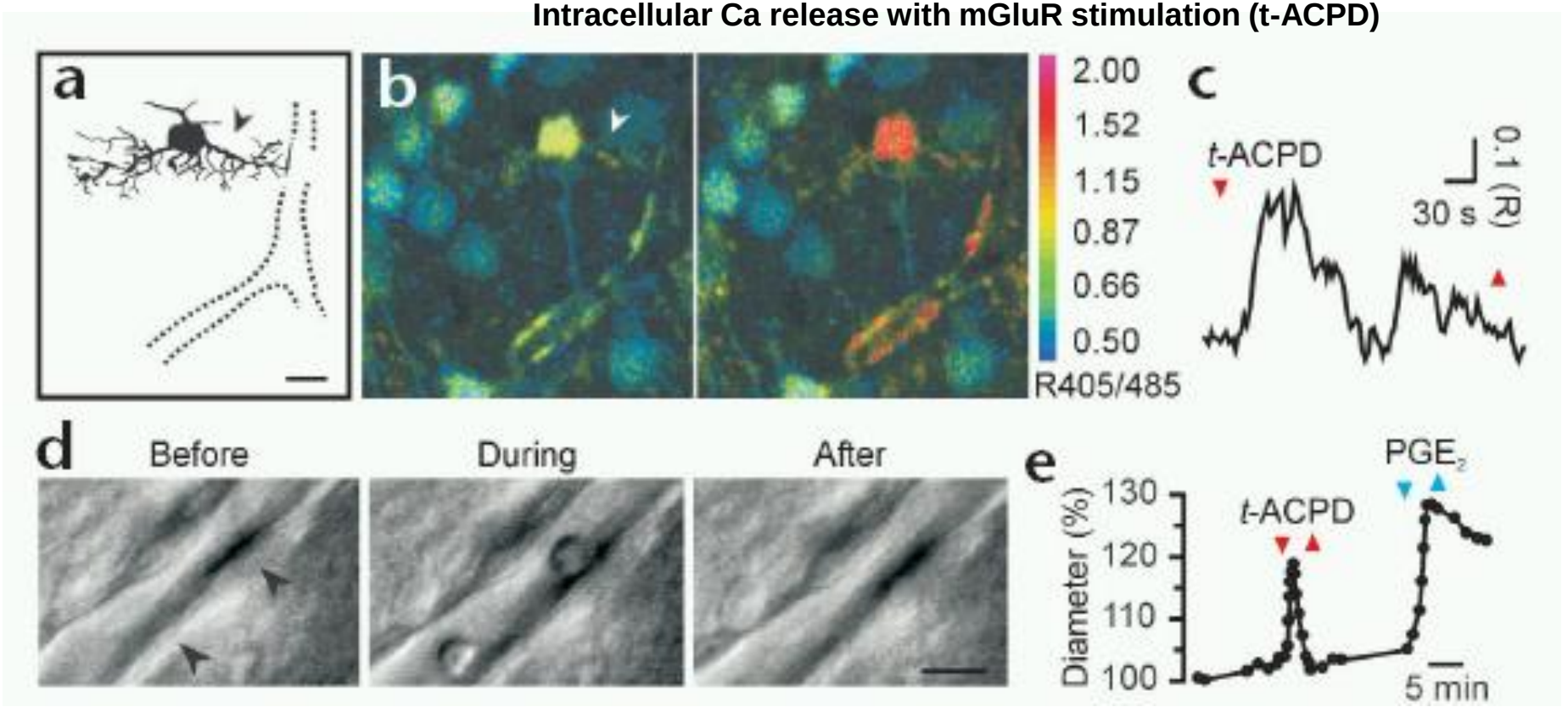
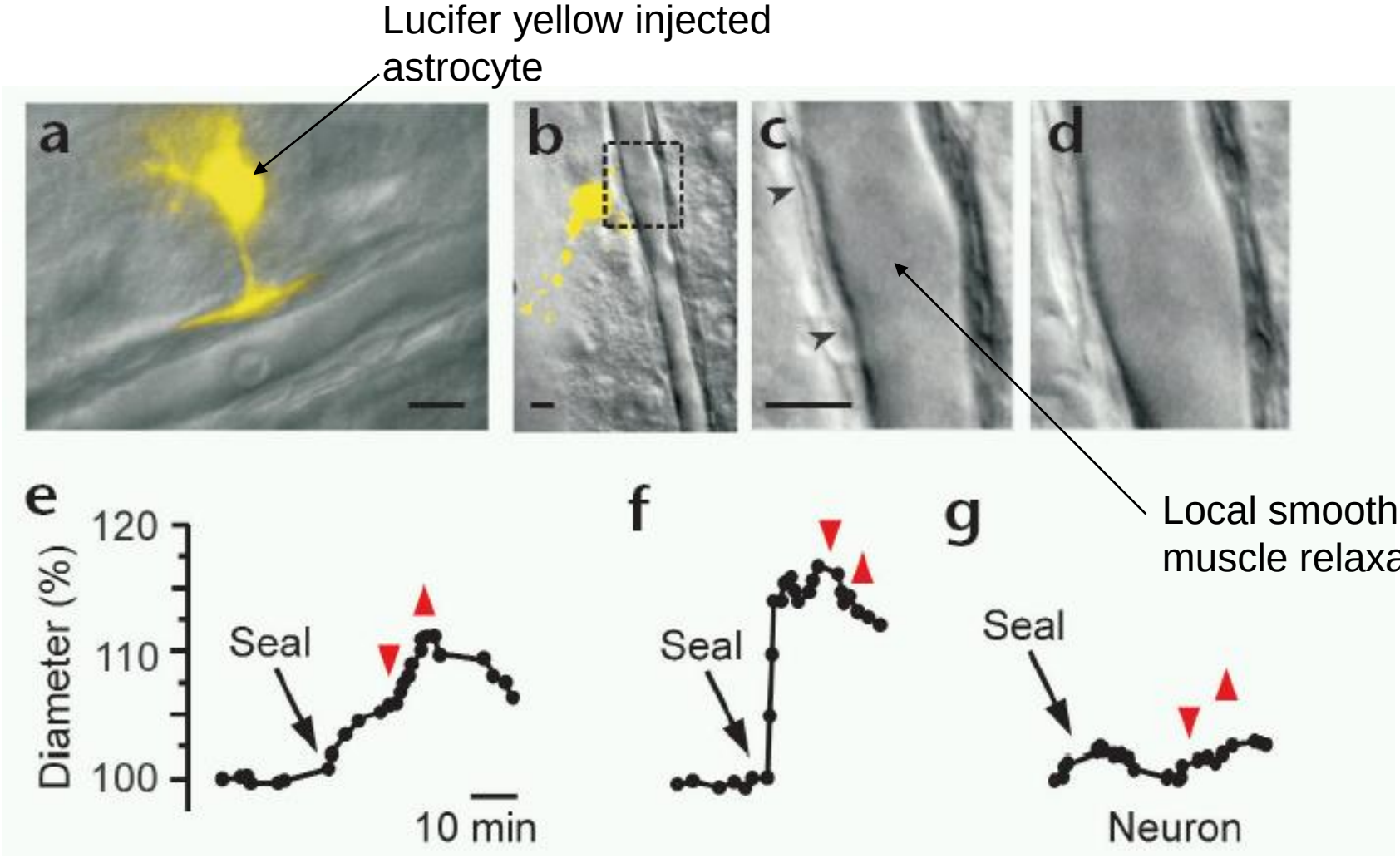
Nature Neurosci. 6 (2003) 43

Astrocytes are glutamate responsive and mediate arteriolar smooth muscle control via COX products

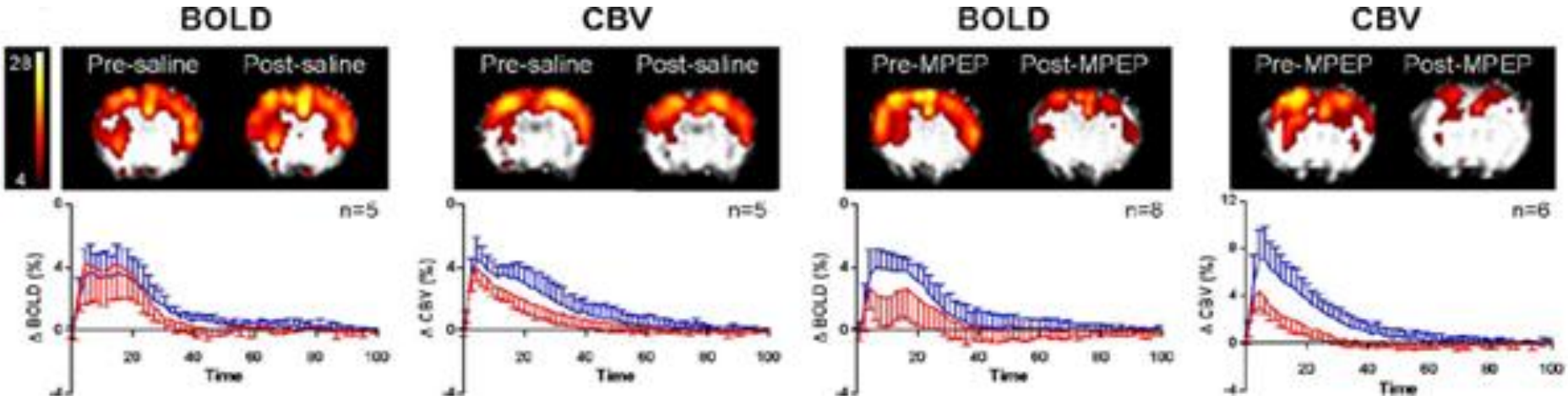
Intracellular Ca release with mGluR stimulation (t-ACPD)



Direct electrical stimulation of astrocyte relaxes arteriolar smooth muscle



Modulation of BOLD response from direct cortical stimulation by selective astrocyte metabotropic GluR5 inhibition

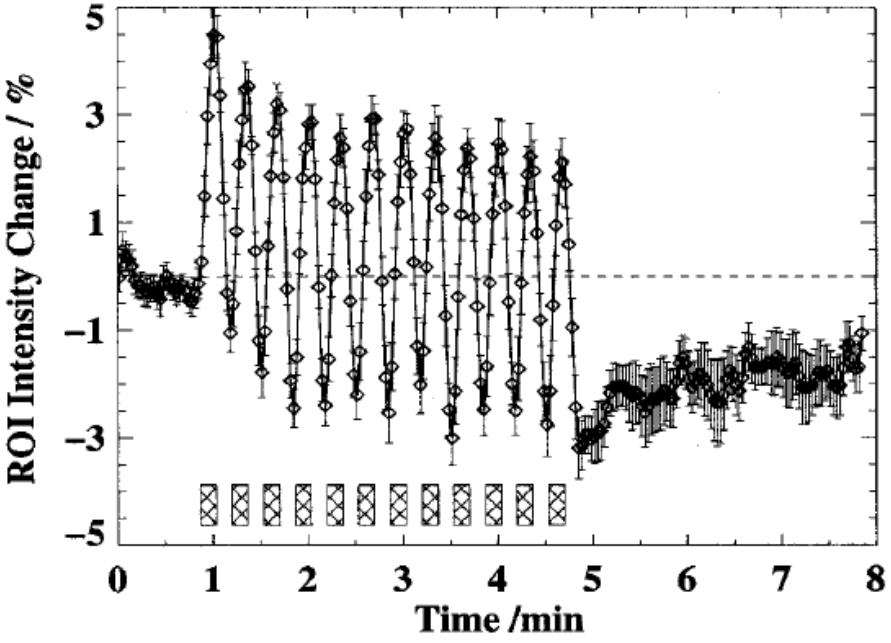


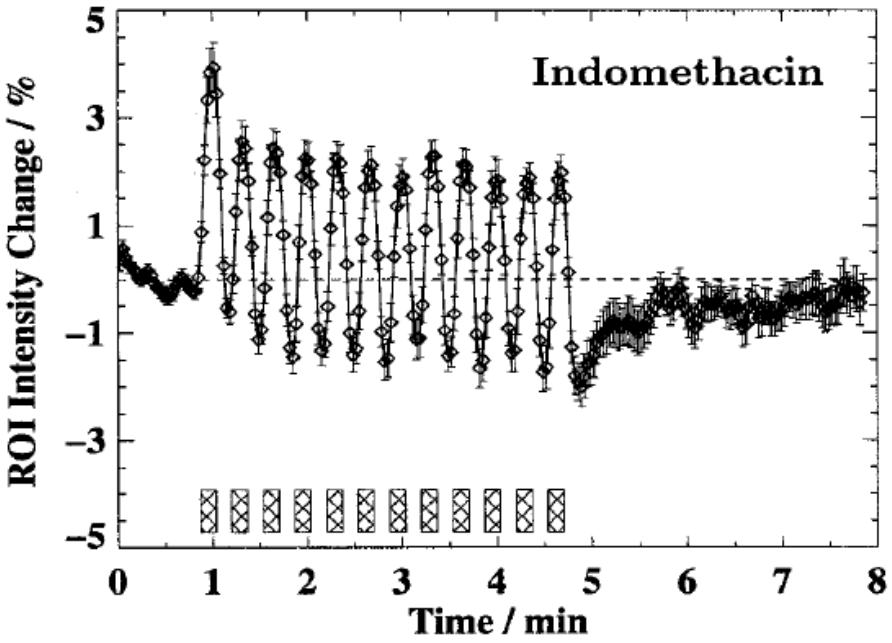
Saline

mGluR5 anatogonist
[2-methyl-6-(phenylethynal)-pyridine (MPEP)]

Sloan et al. Neuroimage, epub

Pharmacological modulation of neurovascular coupling

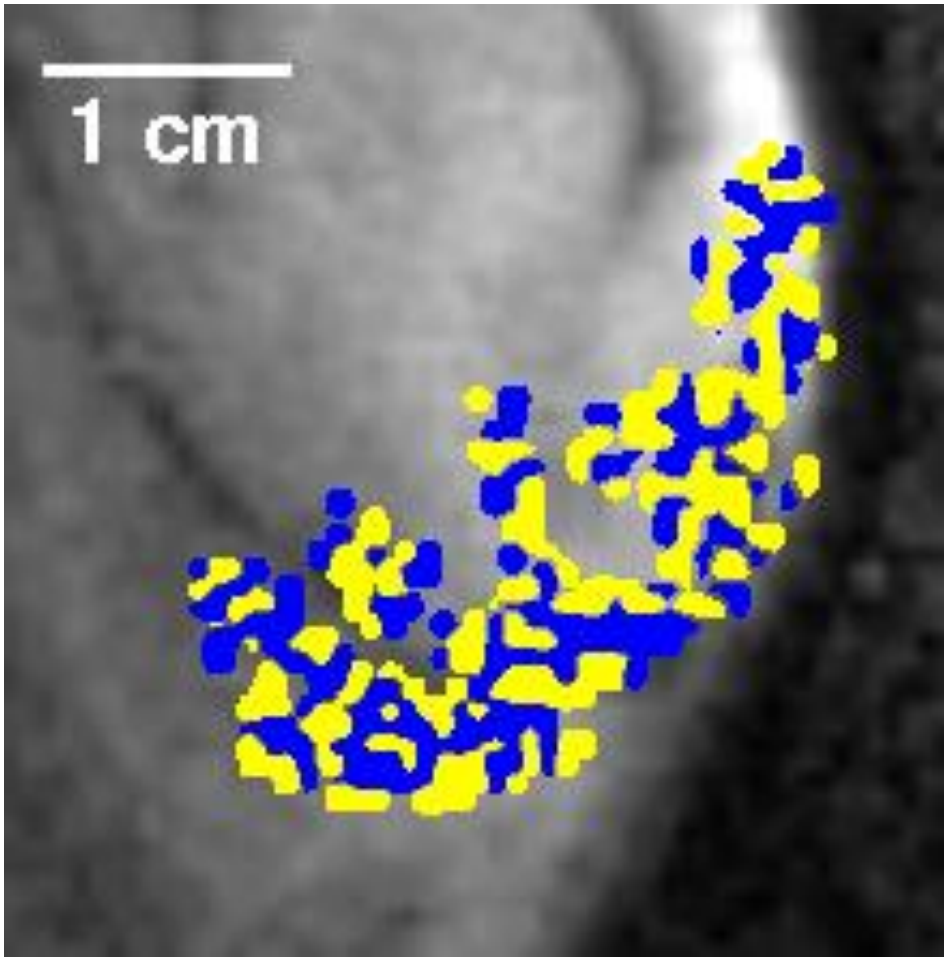




~45% decrease in BOLD response

Bruhn et al. J Magn Reson Imaging 13(2001)325-334

What is the lowest level for control of local blood flow in the brain?

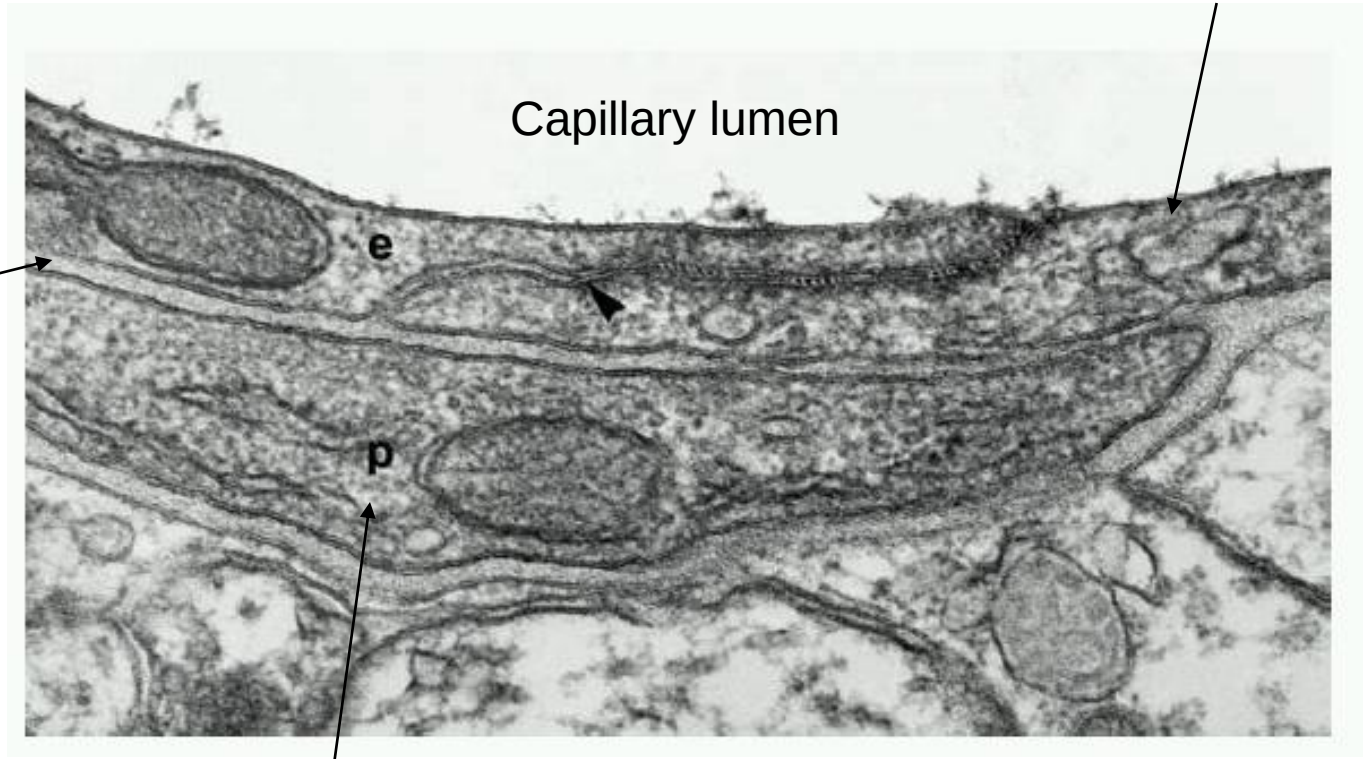


Functional activation of optical dominance columns in the human visual cortex

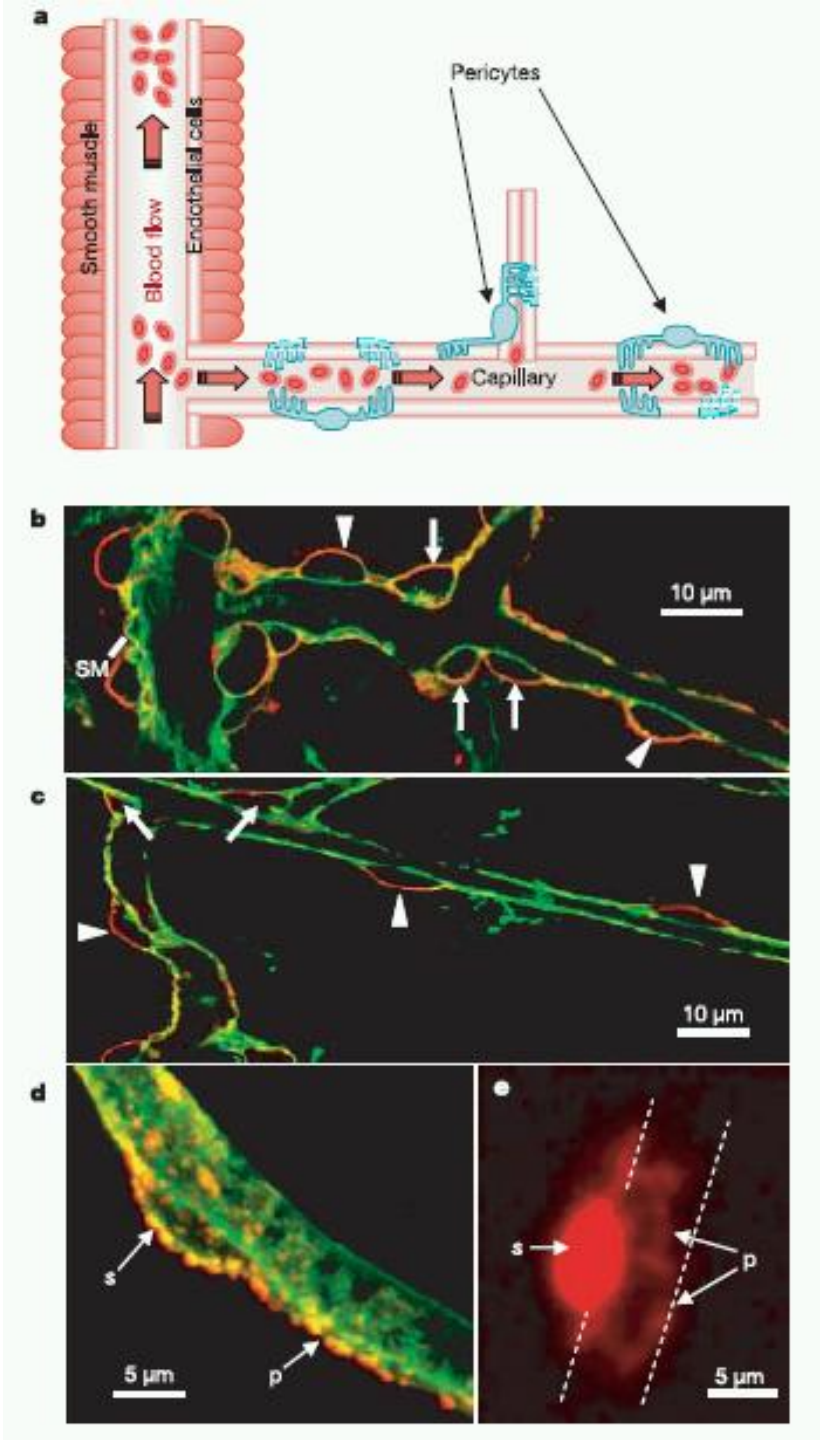
Courtesy of Prof. R. Menon, Univ. West Ontario, Canada

Neurovascular control of capillary flow?

A focus on the pericyte



S. Nag Meth.Molec.Med. 89, 3



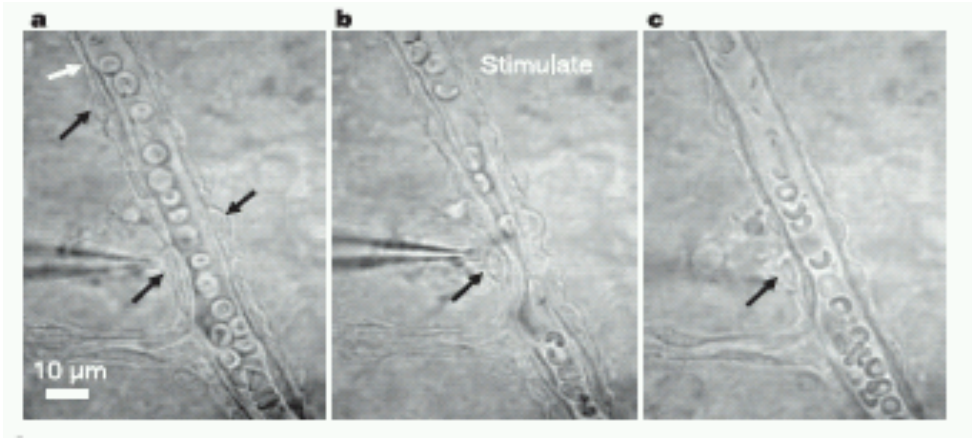
Pericytes are found along capillaries and at junctions

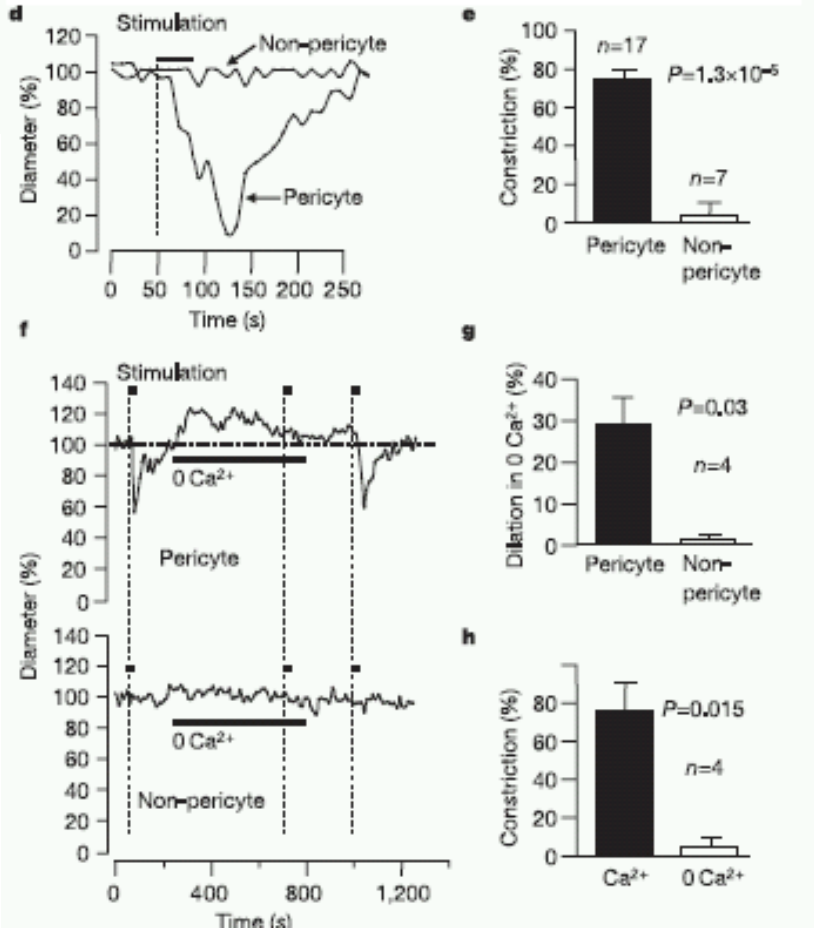
nature Vol 443|12 October 2006|doi:10.1038/nature05193

LETTERS

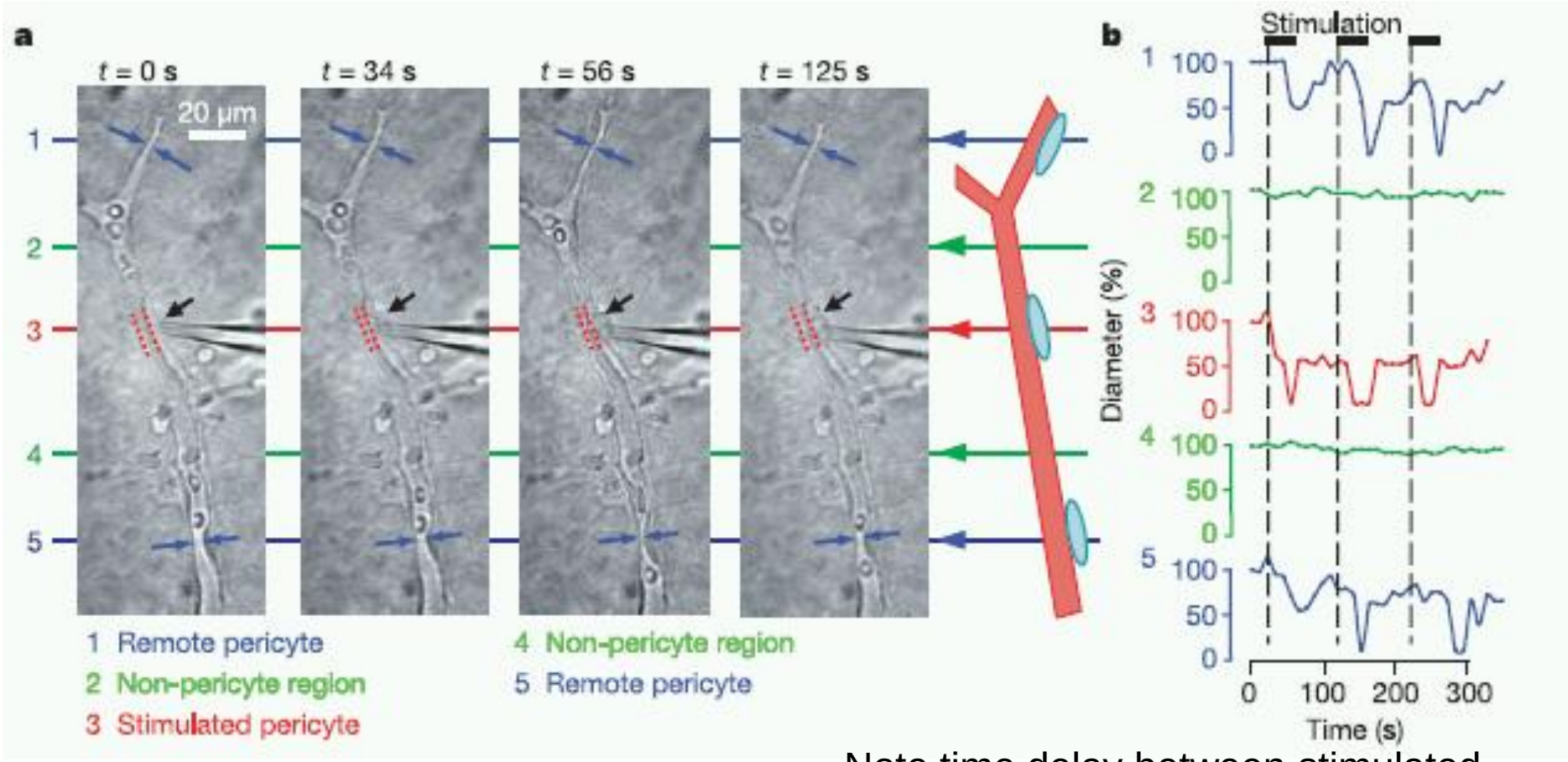
Bidirectional control of CNS capillary diameter by pericytes

Claire M. Peppiatt[1]*, Clare Howarth[1]*, Peter Mobbs[1] & David Attwell[1]



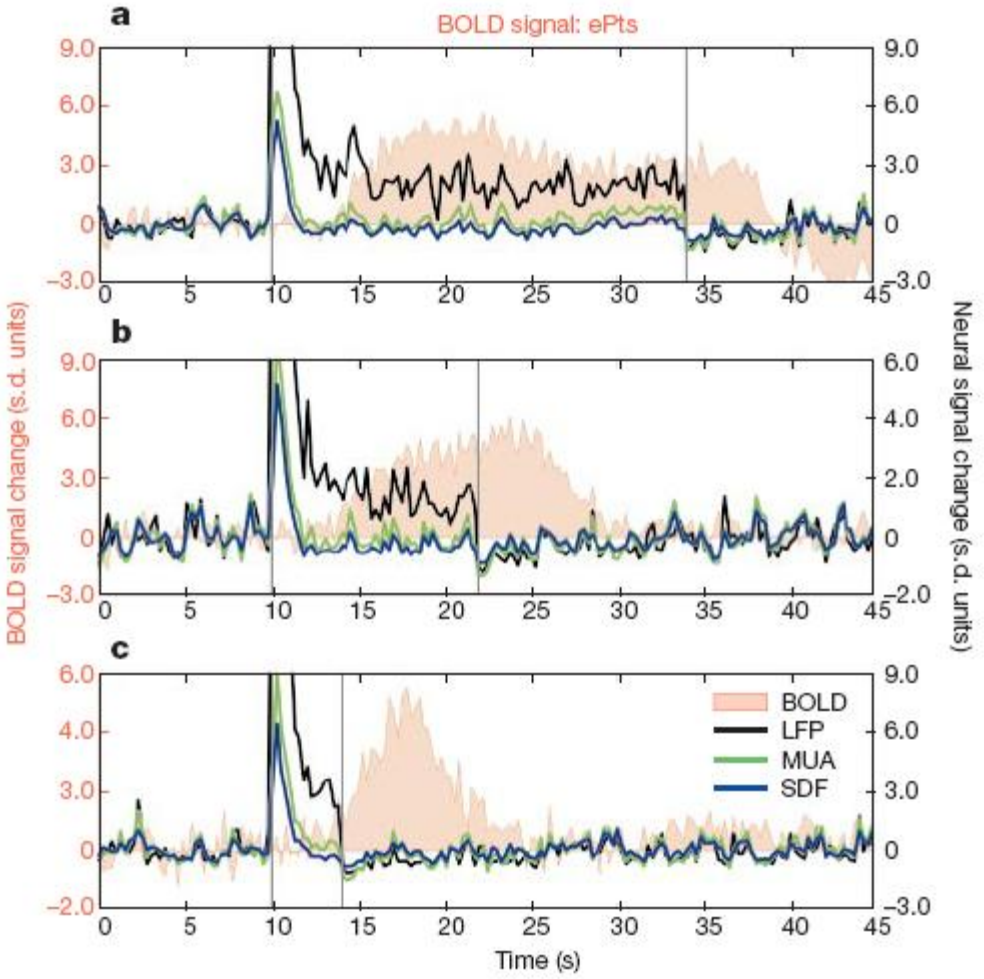


Propagation of contractile waves between pericytes along a capillary



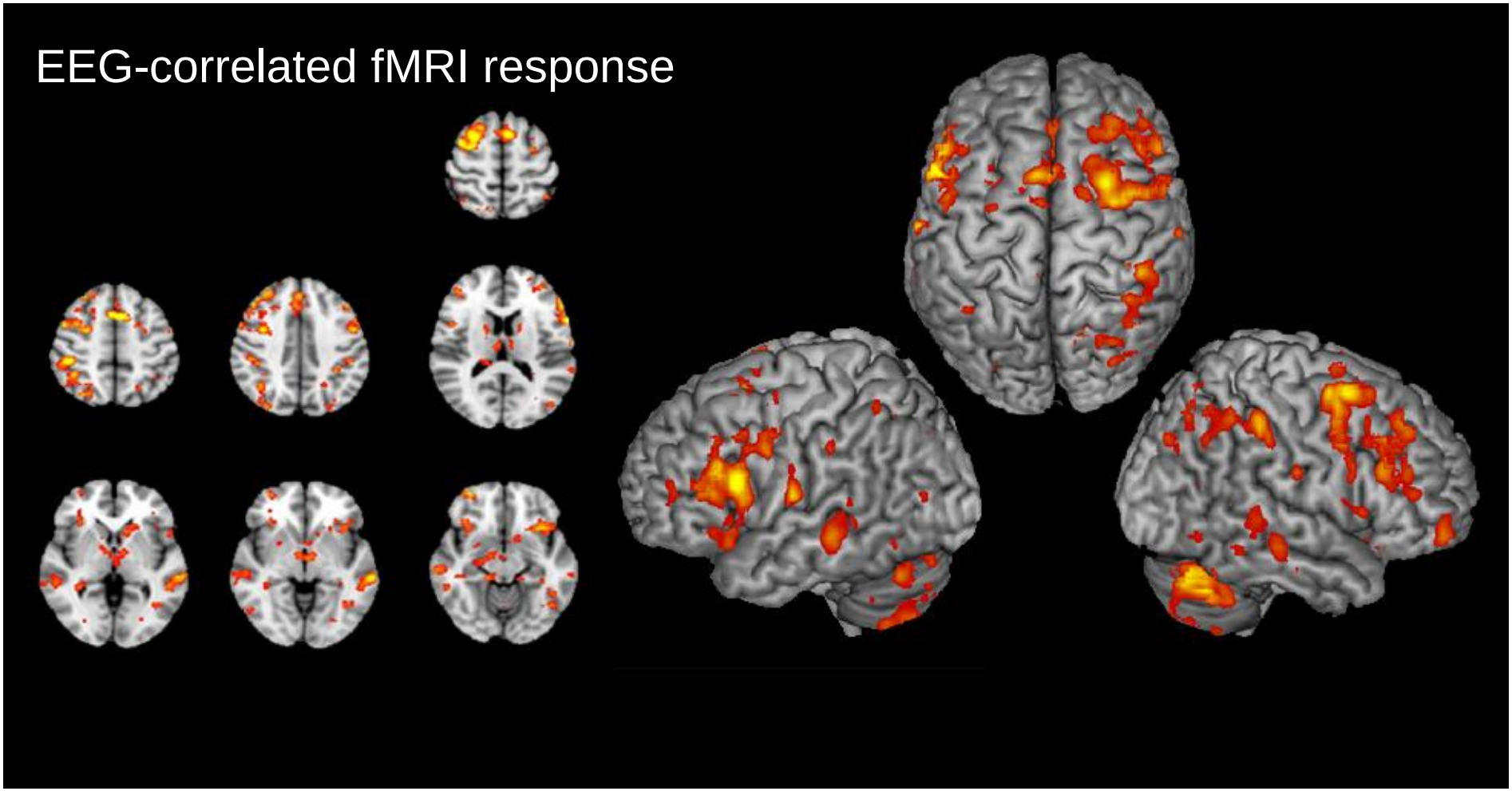
Note time delay between stimulated and “downstream” pericyte

BOLD signal correlates with local field potential (LFP)- reflecting presynaptic changes- not post-synaptic multiple unit spiking activity (MUA)



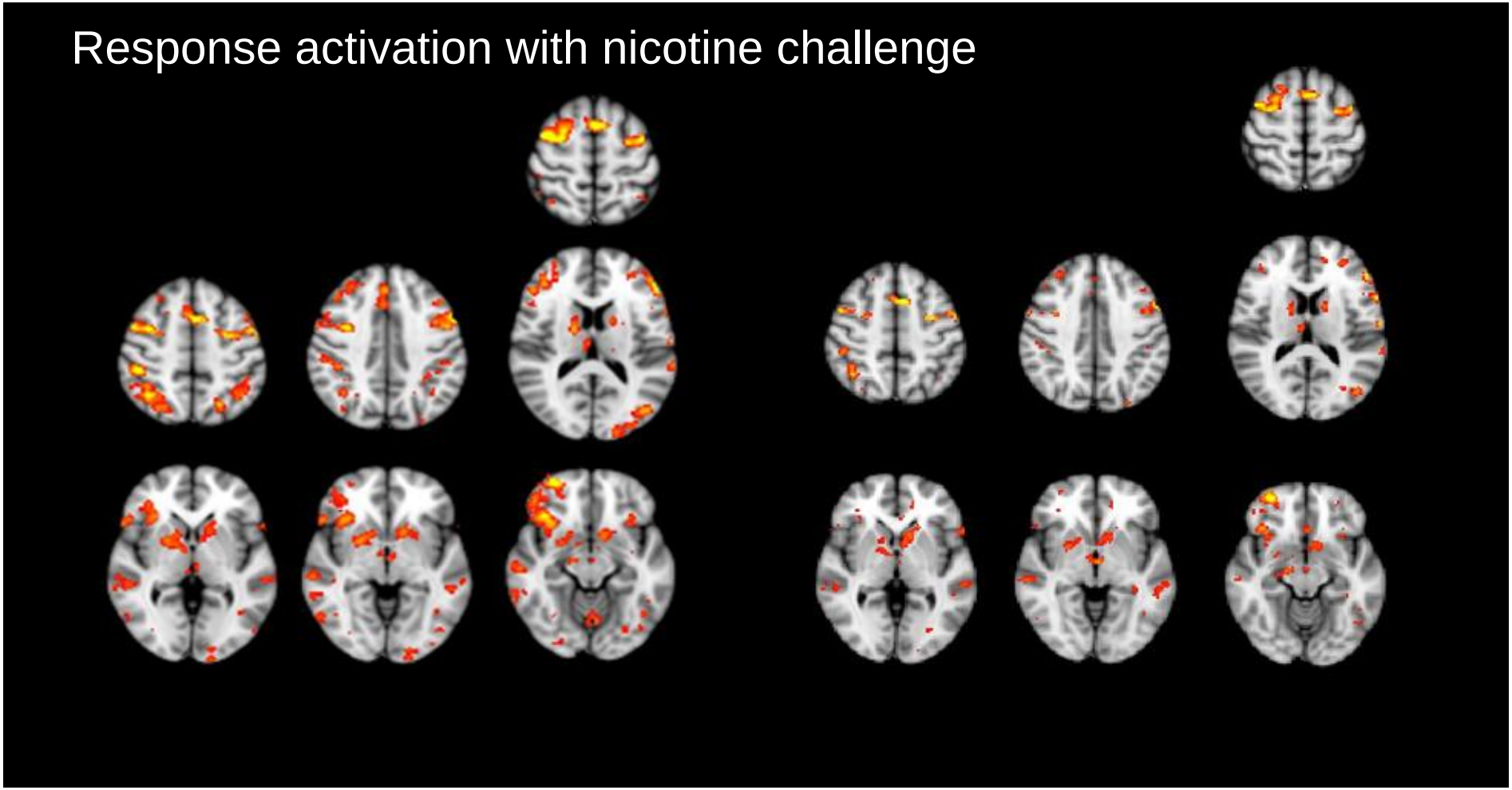
Logothetis et al. Nature 412:150

Formal demonstration that BOLD responses are related to event related electrophysiological dynamics



Data on file, GlaxoSmithKline Consumer Healthcare.

Standard and EEG-correlated BOLD responses identify identical patterns of brain activation



Data on file, GlaxoSmithKline Consumer Healthcare.

Summary

- Sherrington introduced the concept of cerebral local blood flow control related to neuronal activity that underlies most functional brain imaging
- The Sherringtonian mechanism has been modified since to account for apparent lack of a “demand”-lead
- Control appears to be mediated by local neurotransmitter release, interaction with astrocytes (arteriolar) and pericytes (capillaries) and propagation of depolarisations along glial and pericyte networks
- Glutamate release acting at metabotropic receptors plays a central role
- Activation changes correlate well with both near- and far-field potentials