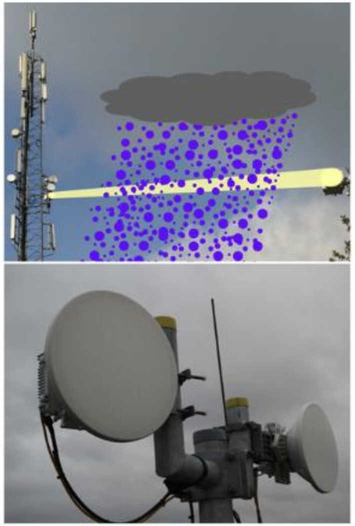
# BOLD signal physiology

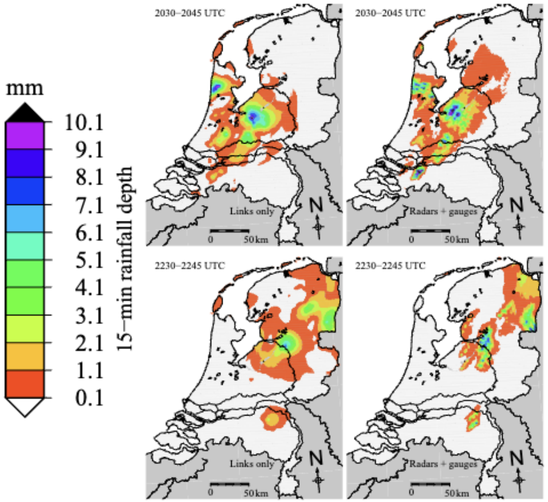
# Let’s talk about (B)rain mapping!

**Measuring precipitation using cell phone towers**
Overeem et al. 2013

Rain attenuates
cell phone signals



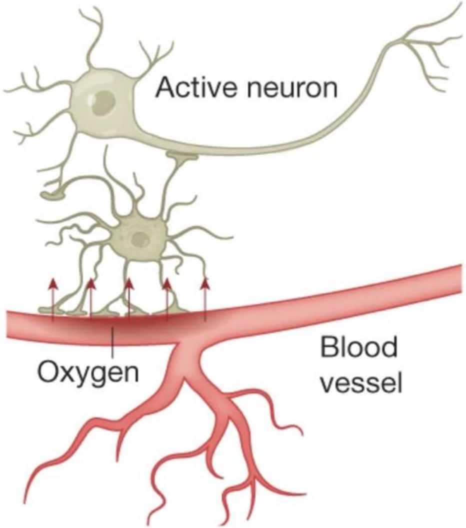
Thousands of radio towers
in the Netherlands




By measuring
the attenuation
of radio signals
between towers,
the dynamics of
precipitation can
be mapped across
space and time

**Scientific measurements are often indirect, but they still allow key insights into the spatiotemporal dynamics of complex systems.**

# Neurovascular coupling



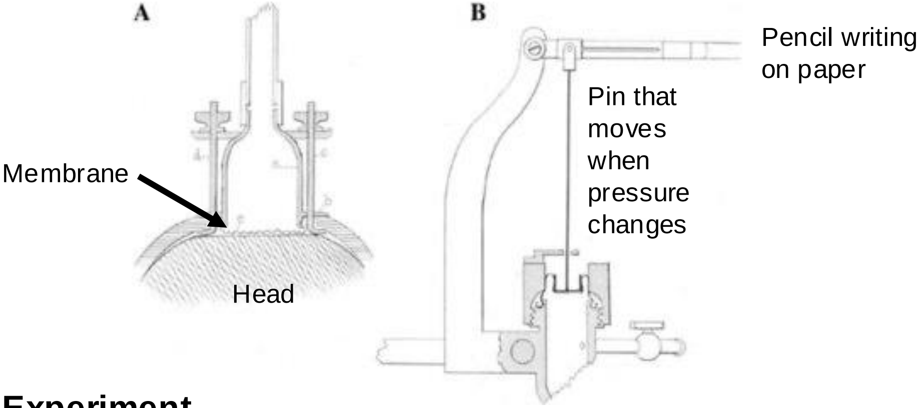

Neural activity triggers changes in cerebral blood flow,
ensuring rapid delivery of oxygen (etc) to active neural tissue

# **Neurovascular coupling:** The discovery

Initial observations of changes in blood flow in response to increased brain activity in animals

Roy & Sherrington 1890, J.Physiol

**Roy & Sherrington**
hanging out in front of the lab




**Experiment**
Measuring cranial pressure changes following peripheral nerve stimulation

## Key observation

The pressure in the head changes when peripheral nerves are stimulated, linking neural activity to cerebral blood flow (in the 1890s!)

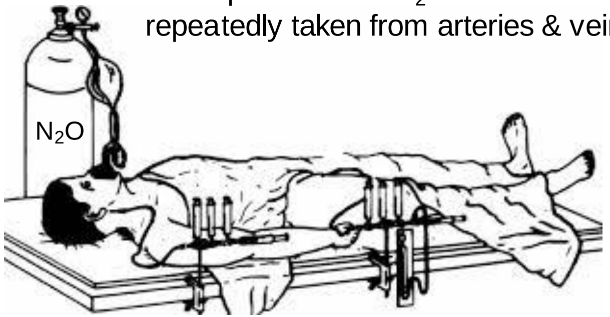
# Neurovascular coupling in humans

Measuring cerebral blood flow (invasively) in humans using the Kety-Schmidt technique

Kety & Schmidt 1945

### Experiment

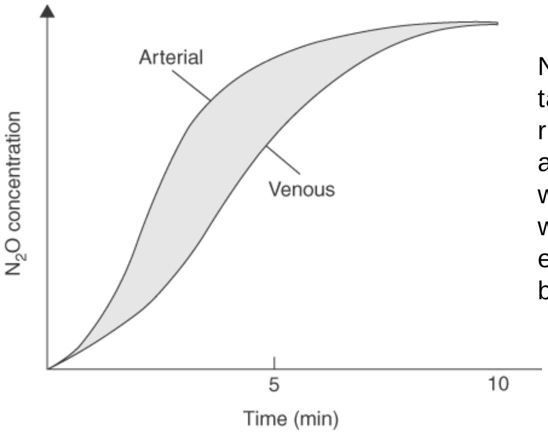
Participant inhales $N_2O$ while blood is repeatedly taken from arteries & veins




Blood from arteries

Blood from veins

### Results




$N_2O$-rich blood takes time to reach the veins, and $N_2O$ diffuses while in the brain, which allows estimating cerebral blood flow

## Key observation

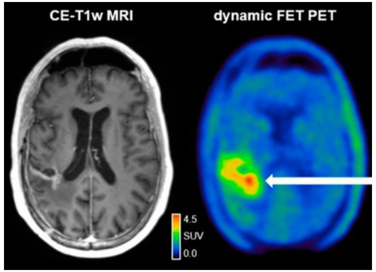
By measuring differences in $N_2O$ concentration in arterial blood (going to the brain) and venous blood (coming from the brain), cerebral blood flow can be estimated and compared across tasks (e.g., rest vs. hyperventilation)

# Development of invasive imaging techniques

fMRI stands on the shoulders of earlier imaging techniques that use tracers to image tissue

## What is a tracer?

Substance introduced into the blood stream that either emits a signal (e.g., Radioactive material) or changes another (e.g., Contrast agents)

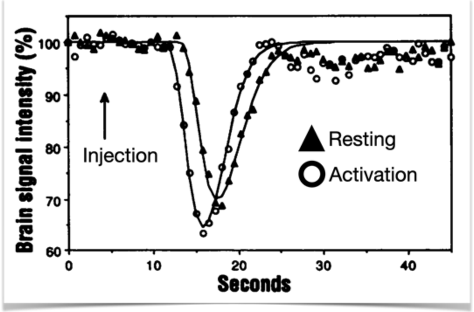



Example 1: **Positron Emission Tomography (PET) Imaging**

Imaging emissions of radioactive material for quantative assessment of metabolism and detection of pathologies with high sensitivity (e.g., cancer).

Example 2: **Gadolinium-enhanced MRI**

Gadolinium is the most paramagnetic element at body temperature (i.e., it affects the magnetic field). Once injected, it allows imaging the cerebral blood volume (CBV) for individual parts of the brain.




Belliveau et al. 1991

## Potential problems?

Health risks due to allergic reactions, radiation damage, tracer accumulation in tissues... Also ethical problems with informed consent!

# Blood oxygenation level dependent (BOLD) signal

Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 9868–9872, December 1990
Biophysics

**Brain magnetic resonance imaging with contrast dependent on blood oxygenation**

**(cerebral blood flow/brain metabolism/oxygenation)**

S. Ogawa, T. M. Lee, A. R. Kay, and D. W. Tank

Biophysics Research Department, AT&T Bell Laboratories, Murray Hill, NJ 07974

*Communicated by Frank H. Stillinger, September 24, 1990 (received for review August 1, 1990)*

**Time Course EPI of Human Brain Function during Task Activation**

Peter A. Bandettini,* Eric C. Wong,* R. Scott Hinks,† Ronald S. Tikofsky,* and James S. Hyde*

** Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226; and † Applied Science Laboratory, GE Medical Systems, Waukesha, Wisconsin 53288*

Received February 5, 1992; revised March 31, 1992; accepted March 31, 1992

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*

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 5951–5955, July 1992
Neurobiology

**Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging**

**(cerebral blood flow/blood oxygenation/visual cortex/positron emission tomography/magnetic susceptibility)**

Seiji Ogawa†, David W. Tank†, Ravi Menon‡, Jutta M. Ellermann‡, Seong-Gi Kim‡, Hellmut Merkle‡, and Kamil Ugurbil‡

†Biological Computation Research Department, AT&T Bell Laboratories, 600 Mountain Avenue, Murray Hill, NJ 07974; and ‡Center for Magnetic Resonance Research, University of Minnesota Medical School, 385 East River Road, Minneapolis, MN 55455

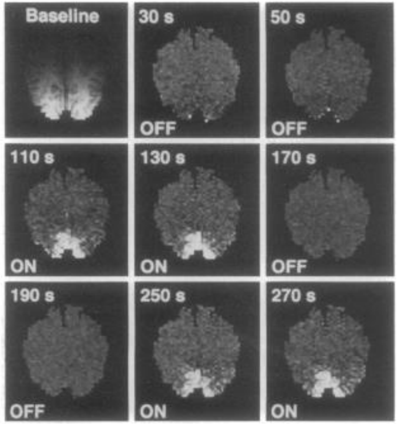
*Communicated by R. Llinás, March 31, 1992*

For historical overview, see Bandettini 2012 (“20 years of fMRI”)

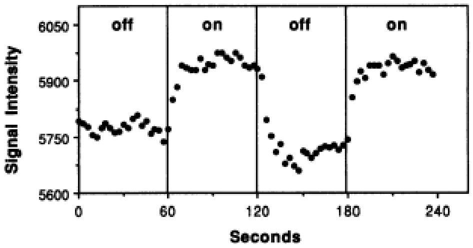
# Blood oxygenation level dependent (BOLD) signal

## Visual stimulation increases MRI signal intensity in occipital lobe

Kwong et al. 1992

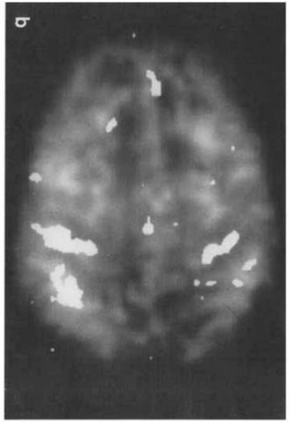


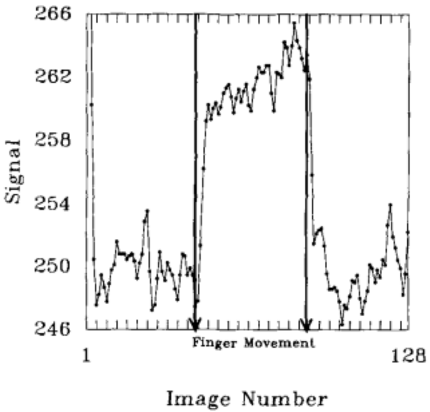

Photic Stimulation -- GE Images




## Finger tapping related activity in motor cortex

Bandettini et al. 1992




**An endogenous contrast agent for non-invasive imaging of human brain activity**

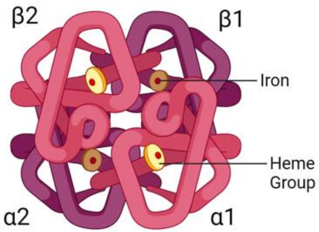
(a new research field was born!)

# Blood oxygenation level dependent (BOLD) signal

**Erythrocytes**
contain **hemoglobin**

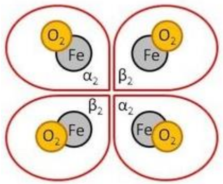
Red blood cells

**Hemoglobin**
contains **iron**

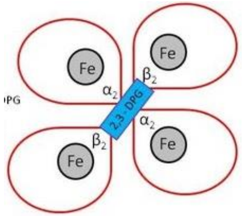



Hemoglobin protein

**Iron** is **oxygenated** or **deoxygenated**




Oxyhemoglobin




Deoxyhemoglobin

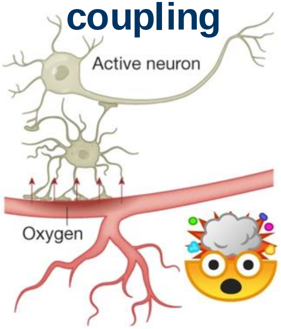
**Oxyhemoglobin is diamagnetic** (i.e., it is repelled by a magnetic field)

**Deoxyhemoglobin is paramagnetic** (i.e., it is attracted to a magnetic field)

**Blood oxygenation interacts with the magnetic field of the scanner, which can be measured!**

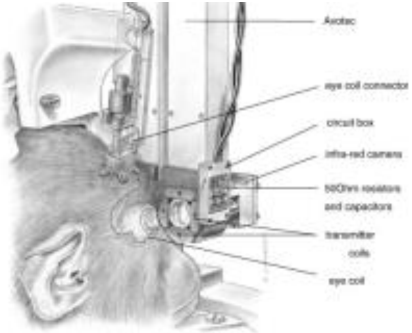
+

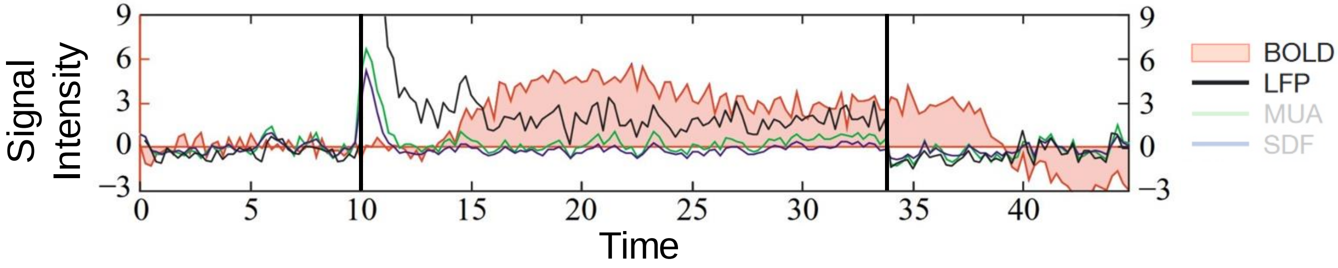
**Neurovascular coupling**



# Blood oxygenation level dependent (BOLD) signal

Linking BOLD to simultaneously recorded local field potentials (LFP, measured with electrodes)



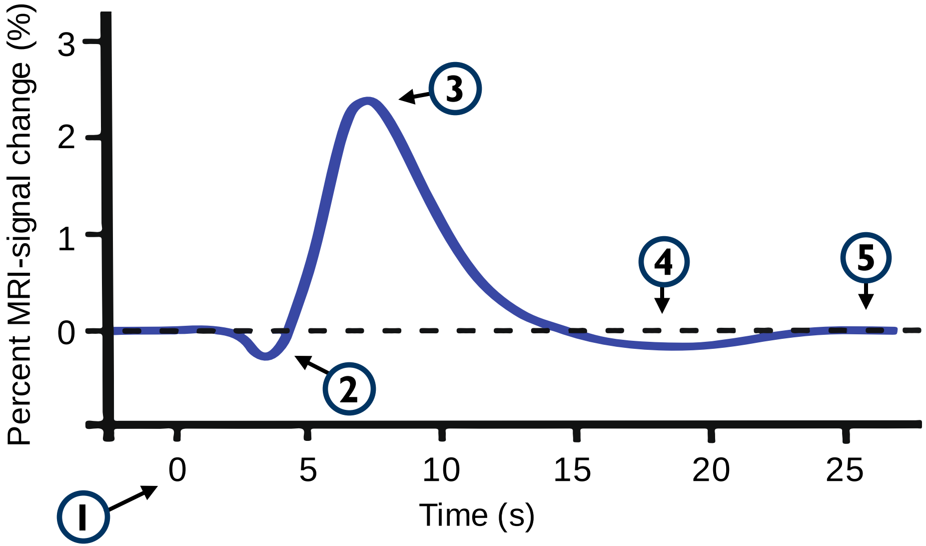

**Key observation**

The BOLD response can be predicted based on the LFP 🤯

Logothetis et al. (2001), Pfeiffer et al. (2004)

# We are in the Brain Imaging course, let's talk about the HRF!

## Hemodynamic response function (HRF)




1) **Neural event**
   Increased neural activity (e.g., following stimulus presentation).

2) **Initial dip (not always observable)**
   Some see a rapid signal decrease, likely reflecting oxygen consumption.

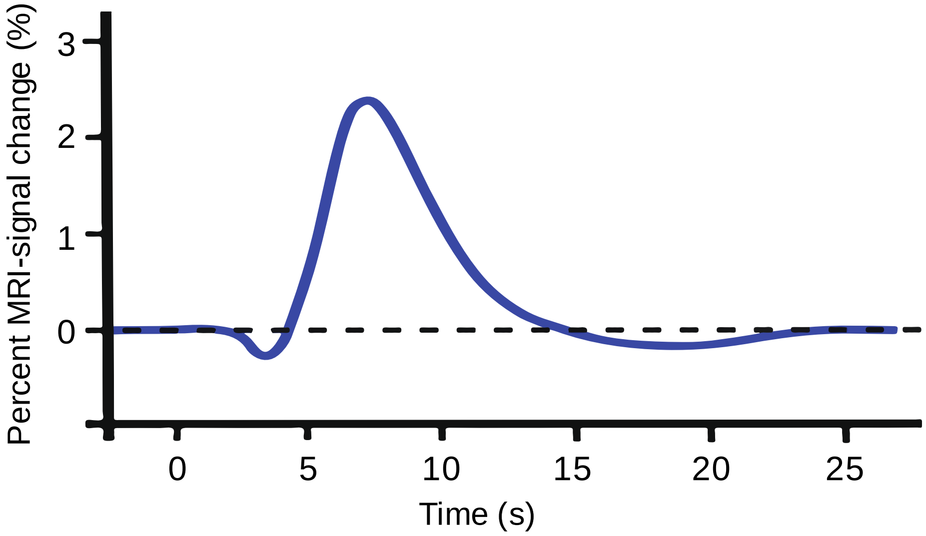
3) **Peak of response**
   Regional blood flow increases disproportionally to the neural event
   («Watering the garden for a flower in need»)

4) **Undershoot**
   Many theories, likely delayed vascular recovery & continued metabolic demand

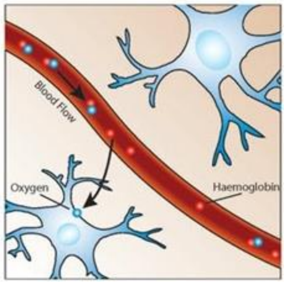
5) **Signal back to baseline**

# We are in the Brain Imaging course, let's talk about the HRF!

## Hemodynamic response function (HRF)

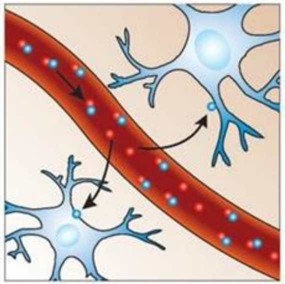



**Rest**




Neural activity causes vessels to dilate, increasing blood flow, and changing the ratio of oxygenated to deoxygenated blood.

**Activation**



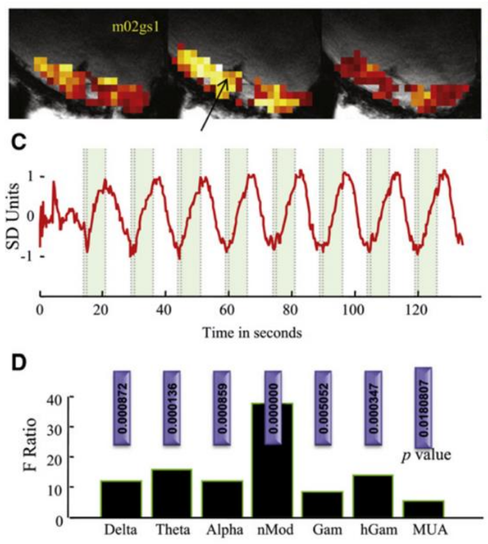
Collectively, these changes are thought to contribute to the observed hemodynamic response.

**Great simple story … or is it?** 🤨

# Why the BOLD signal can be difficult to interpret

# Blood oxygenation level dependent (BOLD) signal

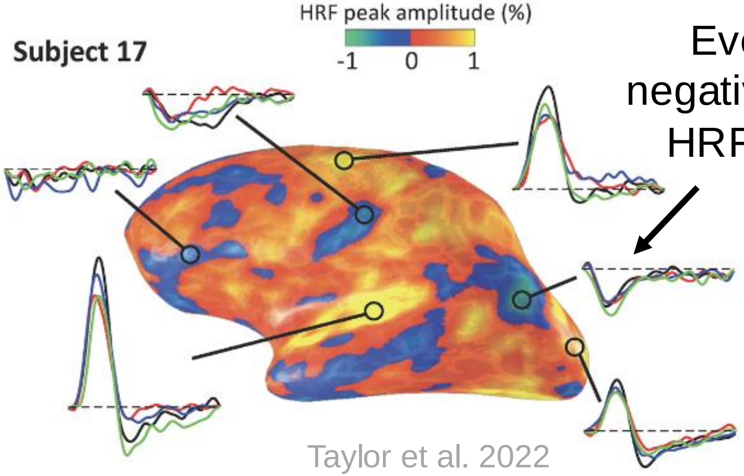
**1) Different LFP frequency bands show distinct correlations with BOLD**




Goense & Logothetis 2008

**2) LFP is thought to reflect the input to a brain circuit, not (only) its output**

**3) The HRF is a compound response of multiple interacting factors** (oxygen metabolism, blood flow, blood volume…), **with varying shape across cortex**

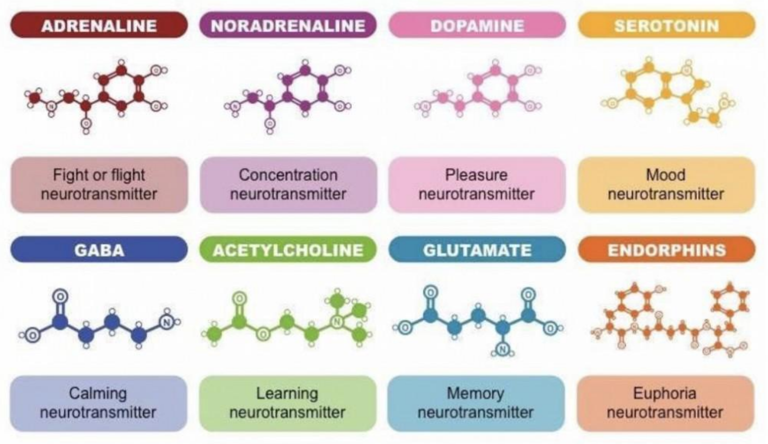



Even negative HRFs!

Taylor et al. 2022

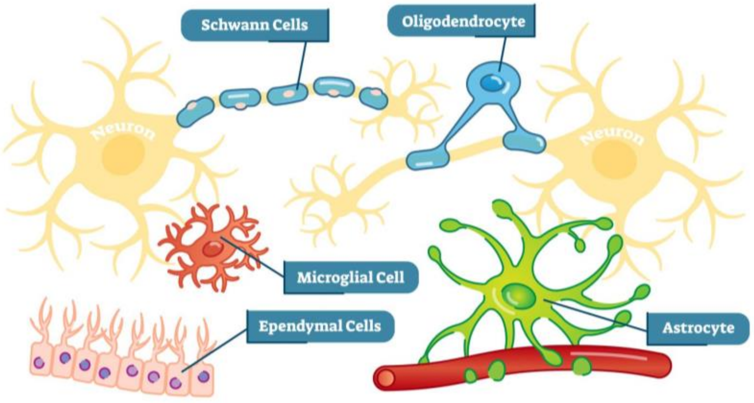
# Blood oxygenation level dependent (BOLD) signal

## 4) Effects of different neurons & transmitters is poorly understood




For example, what about inhibitory interneurons? See e.g., Moon et al. 2021

## 5) Neural activity correlates with non-neural processes (e.g., in glia cells)

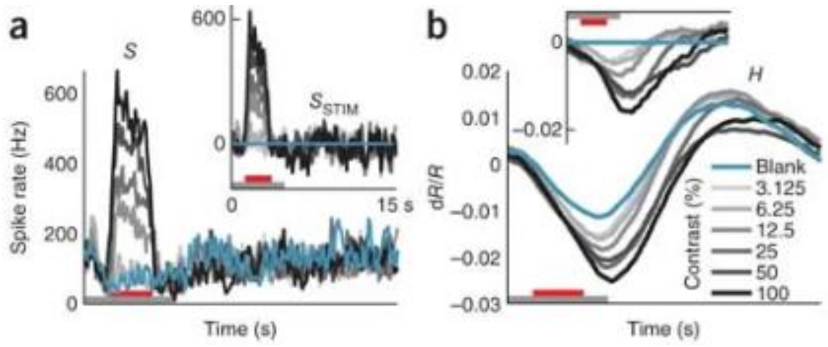



Transmitter re-uptake from synaptic clef is metabolically expensive & can happen many cm away from origin of a spike

# Blood oxygenation level dependent (BOLD) signal

## 6) BOLD responses can occur without neural firing

**Electrophysiology** **fMRI**




Cardoso et al. 2012

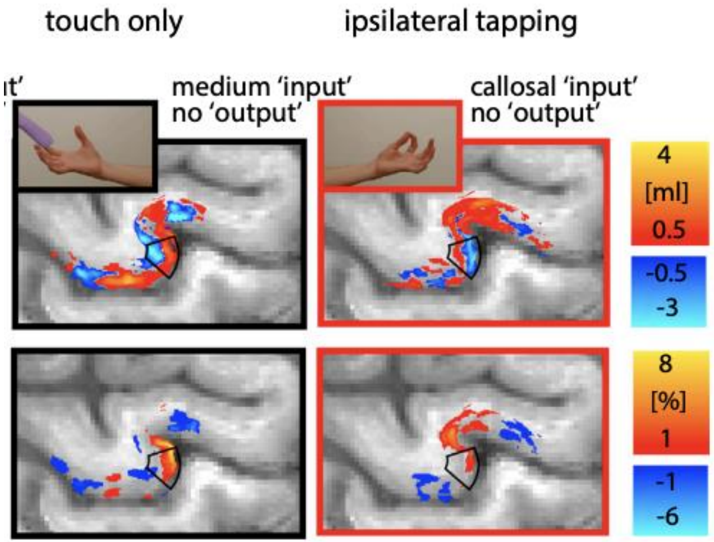
+ More

# There is a lot for you to figure out!

**Advances in Neuroimaging:**
How do we currently study the physiological underpinnings of the BOLD signal?

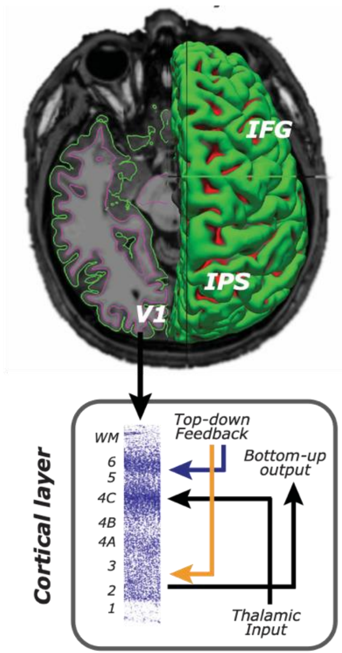
# High-resolution fMRI

Example 1: **"Layer" fMRI**




Huber et al. 2017

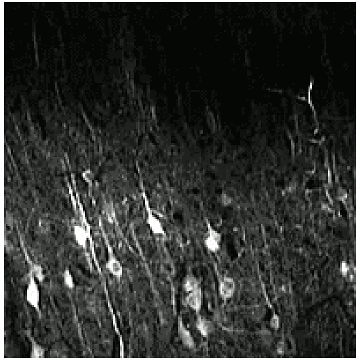
Example 2: **Testing mechanistic predictions***
(e.g., feed-forward vs. feedback signals)



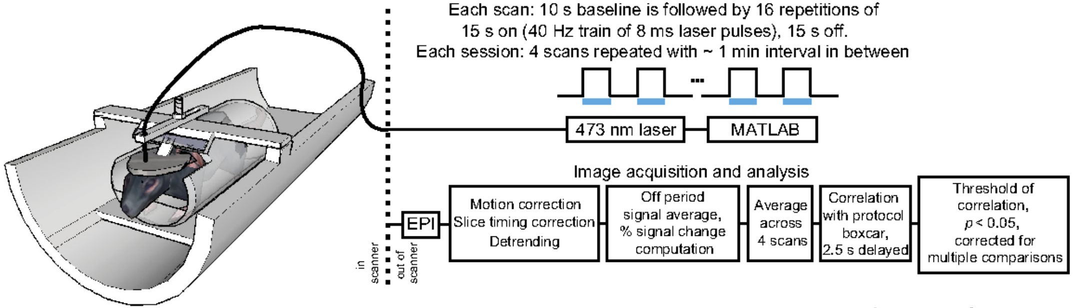

*But devil is in the detail!

# Combining BOLD & other recording or stimulation techniques

Example 3:
**Combined BOLD & Calcium imaging**



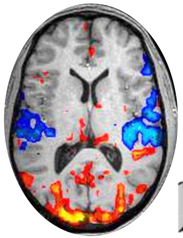
Example 4:
**Awake opto-fMRI in rodents:**
Optogenetic stimulation of specific cell types while measuring the effect on brain-wide BOLD signals

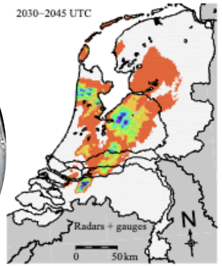



Kahn et al. 2011

# The BOLD signal

- **Indirect measure** of neural activity and other physiological processes (e.g., glia cell function).
- Despite being indirect, it **allows key insights** into the brain's **spatiotemporal dynamics**.
- Neural activity triggers changes in **cerebral blood flow**, in turn affecting the MRI signal due to changes in the **blood's magnetism**.
- Understanding the physiological underpinnings requires clever **experimental design** (see Lecture 2) and a **combination with other techniques** (e.g., ephys).
- **There is more to brain functions than neural activity**
(and there is more to the weather than precipitation)
- **Not every BOLD effect is caused by neurons**
(not every attenuation of radio signals is caused by rain)





# Key terms to remember

- Neurovascular coupling
- Cerebral blood flow
- Kety-Schmidt technique
- Tracer
- PET scanning
- Gadolinum-enhanced fMRI
- BOLD signal
- Endogenous contrast agent
- Hemoglobin
- Oxyhemoglobin
- Deoxyhemoglobin
- Vessel dilation
- Hemodynamic response function (and its 5 stages)
- Local field potential
- Layer fMRI


Image: amberusa.com

# Thanks. See you next time!