Building the Multi-Modal Scaffolding for the fMRI Hemodynamic Response Function

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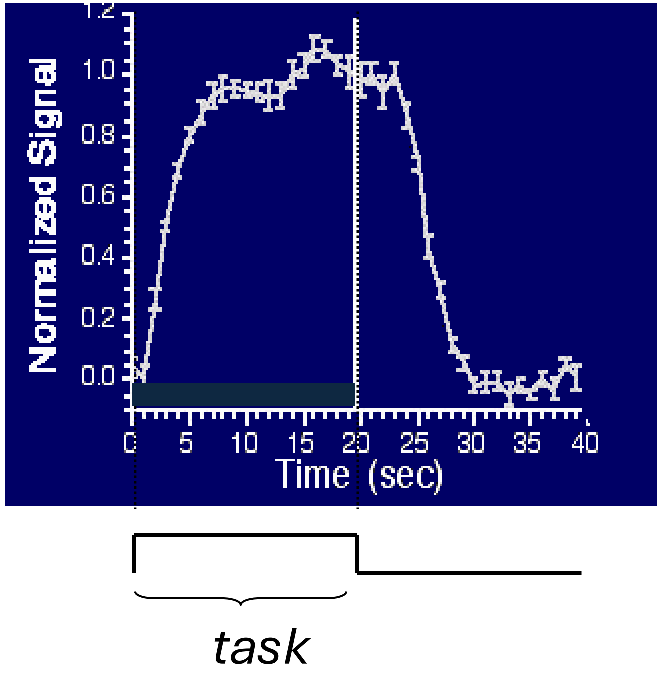
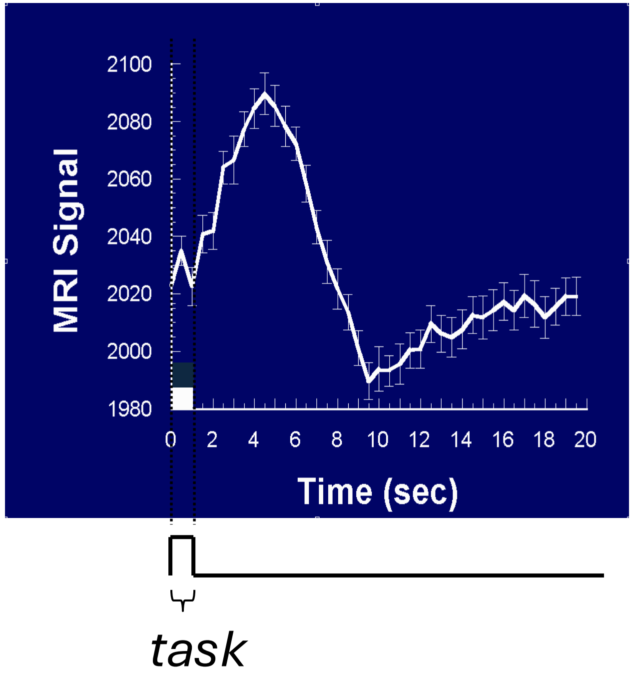
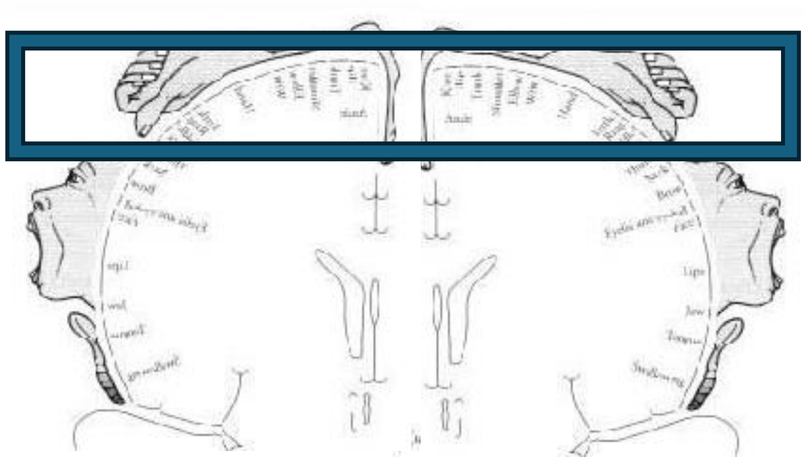
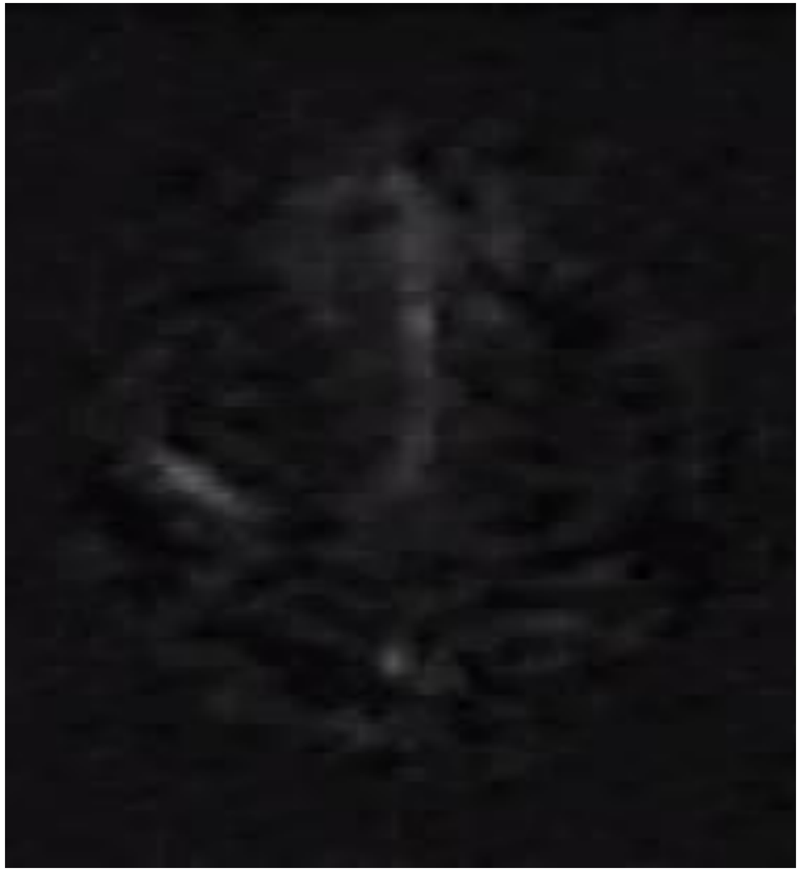
In the Beginning (1991), there was the fMRI signal....









...and we knew it showed brain activity because the ***timing*** and ***spatial location*** aligned with what we already knew about the brain.

...and it was good!

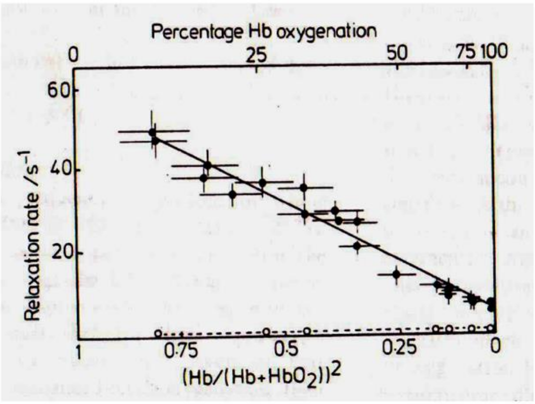
Thanks to Linus Pauling, Seiji Ogawa, and many others, we knew how blood oxygenation influenced the MRI signal…

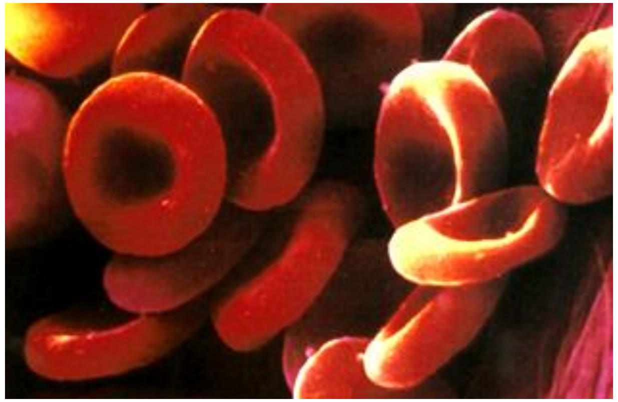
L. Pauling, C. D. Coryell, *Proc.Natl. Acad. Sci. USA 22, 210-216*, 1936.

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

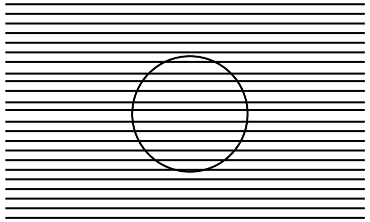
Blood R2 proportional to Oxygenation



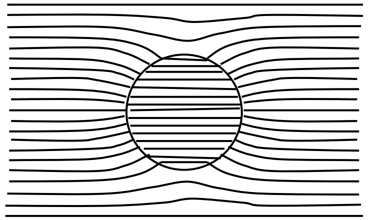


red blood cells

oxygenated



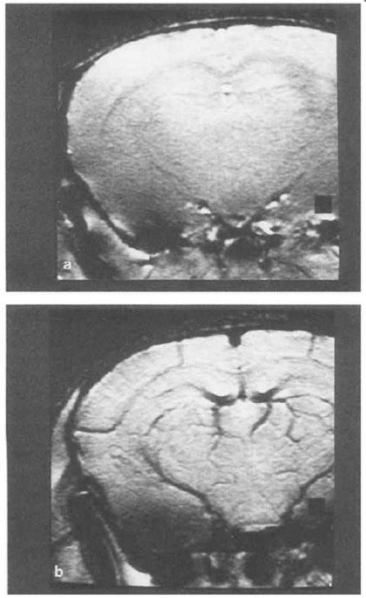
deoxygenated



in vivo

100% O_2

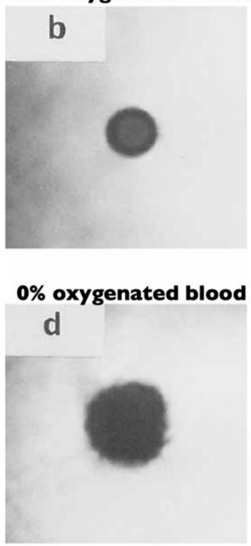
20% O_2



in vitro

100% oxygenated blood

0% oxygenated blood



Thanks to PET scanning (and Peter Fox…and others), we had an idea of the basic mechanism that explained why oxygenation should go up with activation.

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

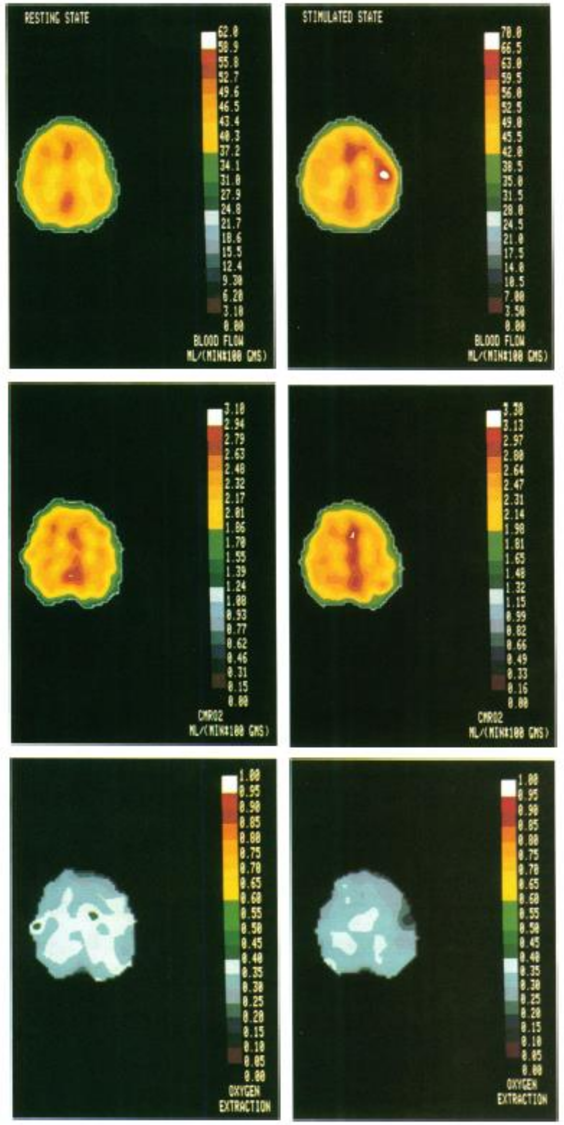
Communicated by Oliver H. Lowry, October 7, 1985

OEF ↓

Therefore…

Blood PO_2 ↑

isons (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.



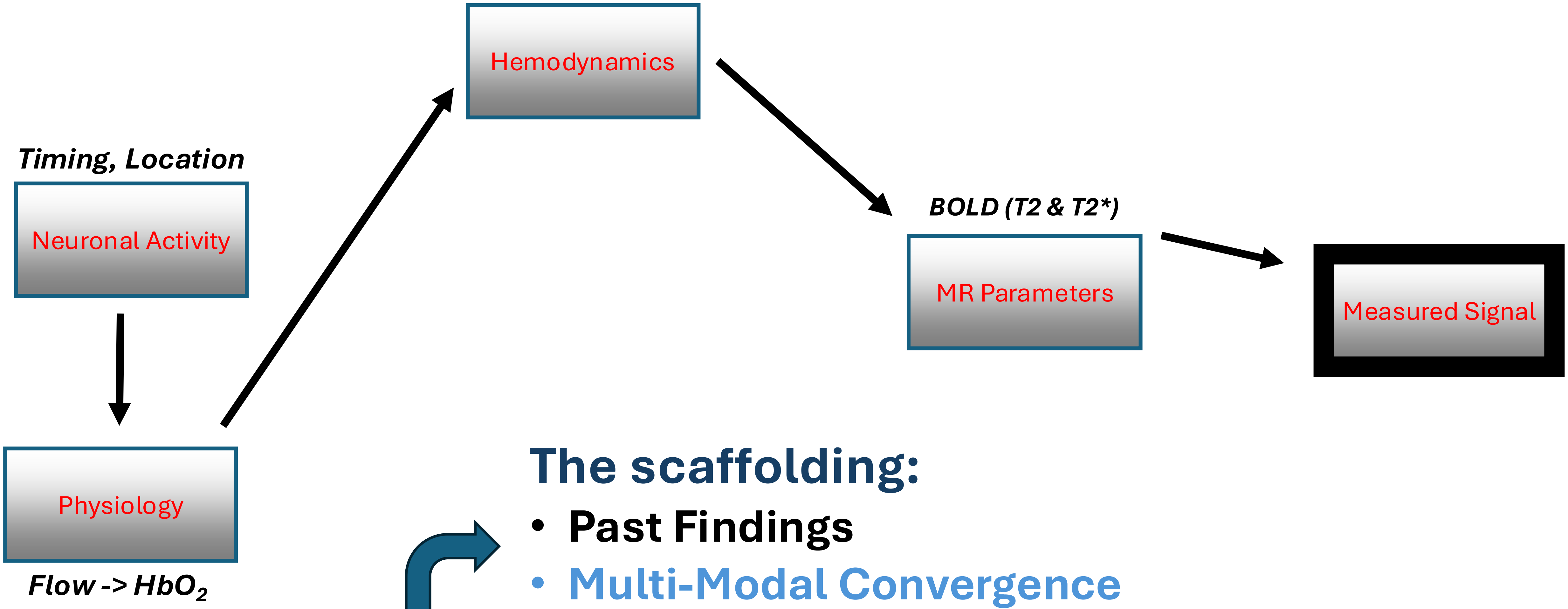
Flow

$CMRO_2$

Oxygen Extraction

We still don't agree on the purpose:
O2 delivery? Metabolite Removal?

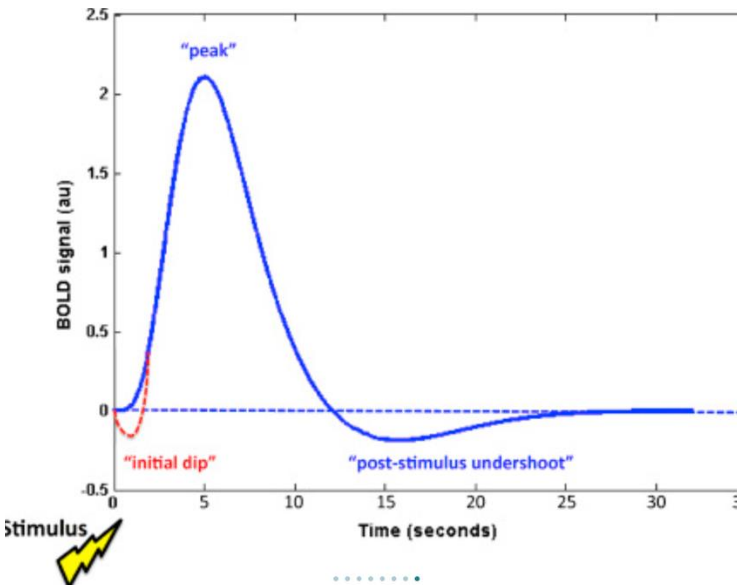
And so the basic scaffolding was put in place....



The scaffolding:

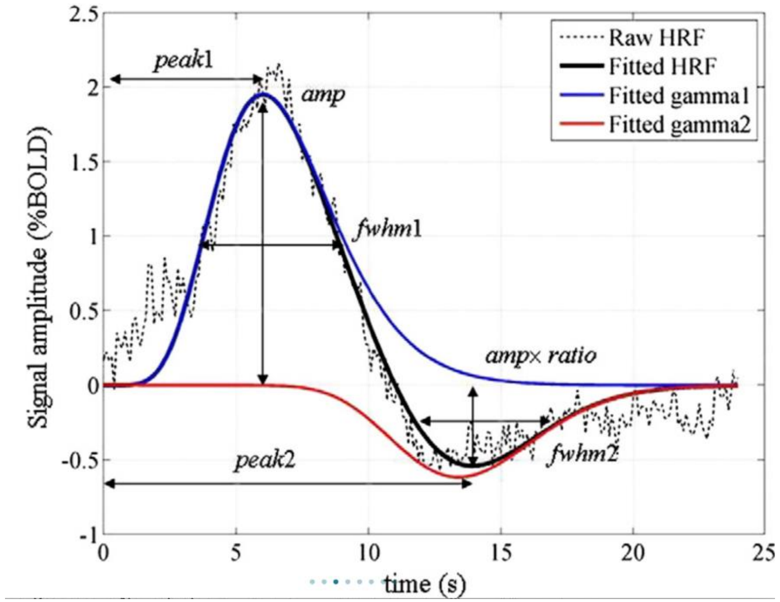
- **Past Findings**
- **Multi-Modal Convergence**
- **Models**
- **New Experiments**
- **Careful Observations**

We looked closer and found some curious features..

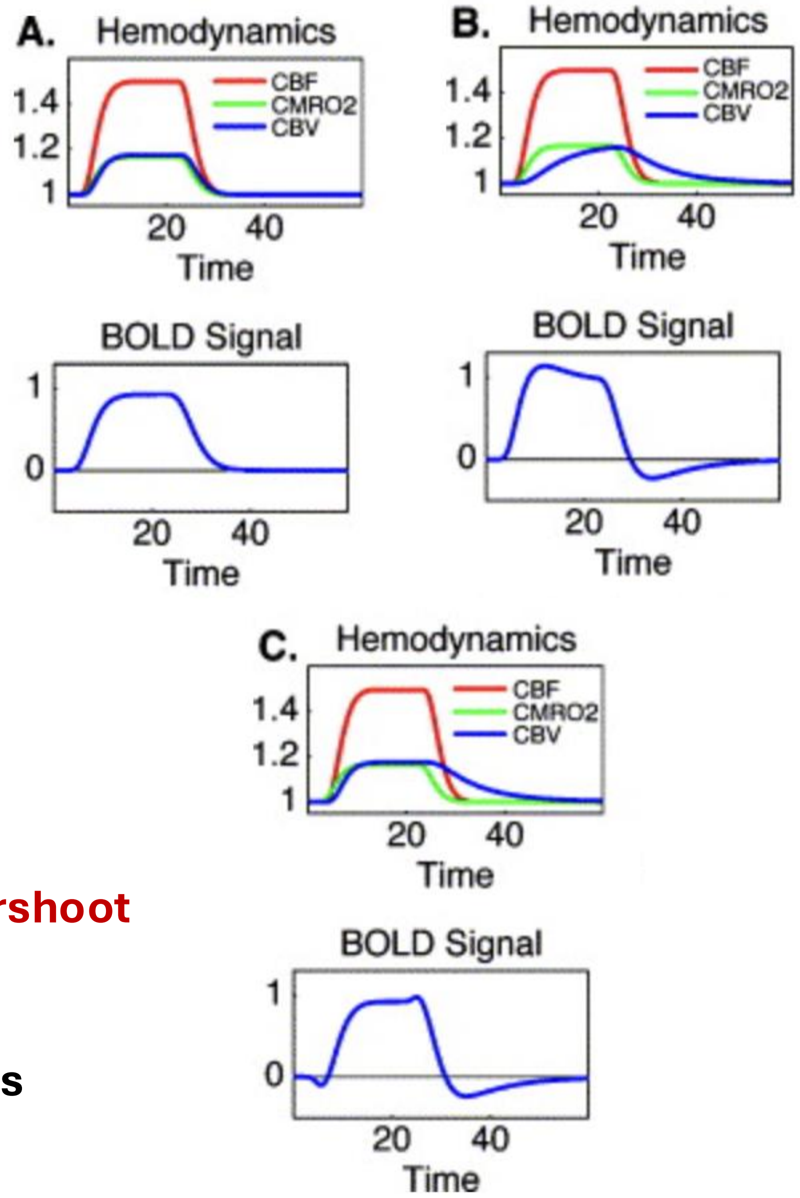


..and we modeled them:

mathematically..



physiologically..

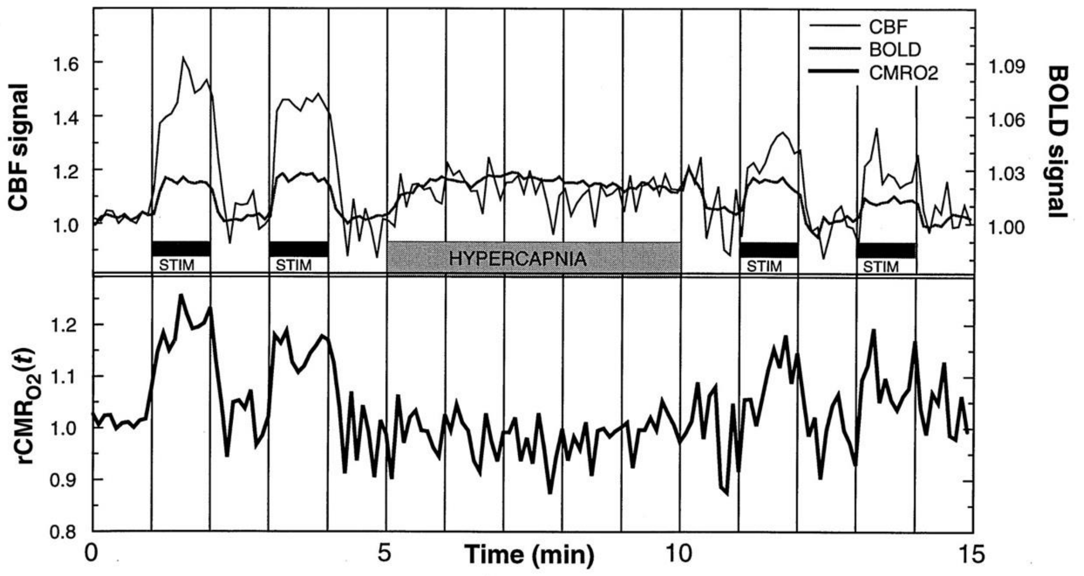


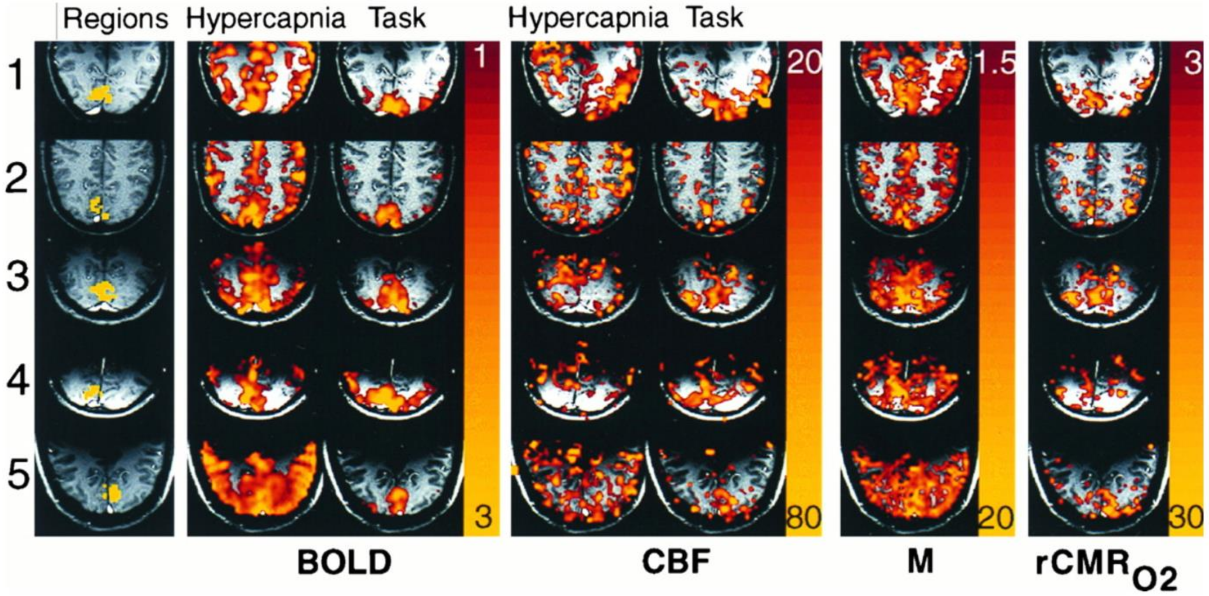
The pre-undershoot issue lost appeal (not repeatable), but the **post undershoot** was heavily debated…flow, CMRO2, volume? Still not fully resolved.

We characterized and are still trying to understand causal mechanisms behind other features : delay, width, variability, magnitude, linearity…

Those models helped in processing most fMRI data (HRF convolution) and to derive $CMRO_2$ ....with the help of another modality:

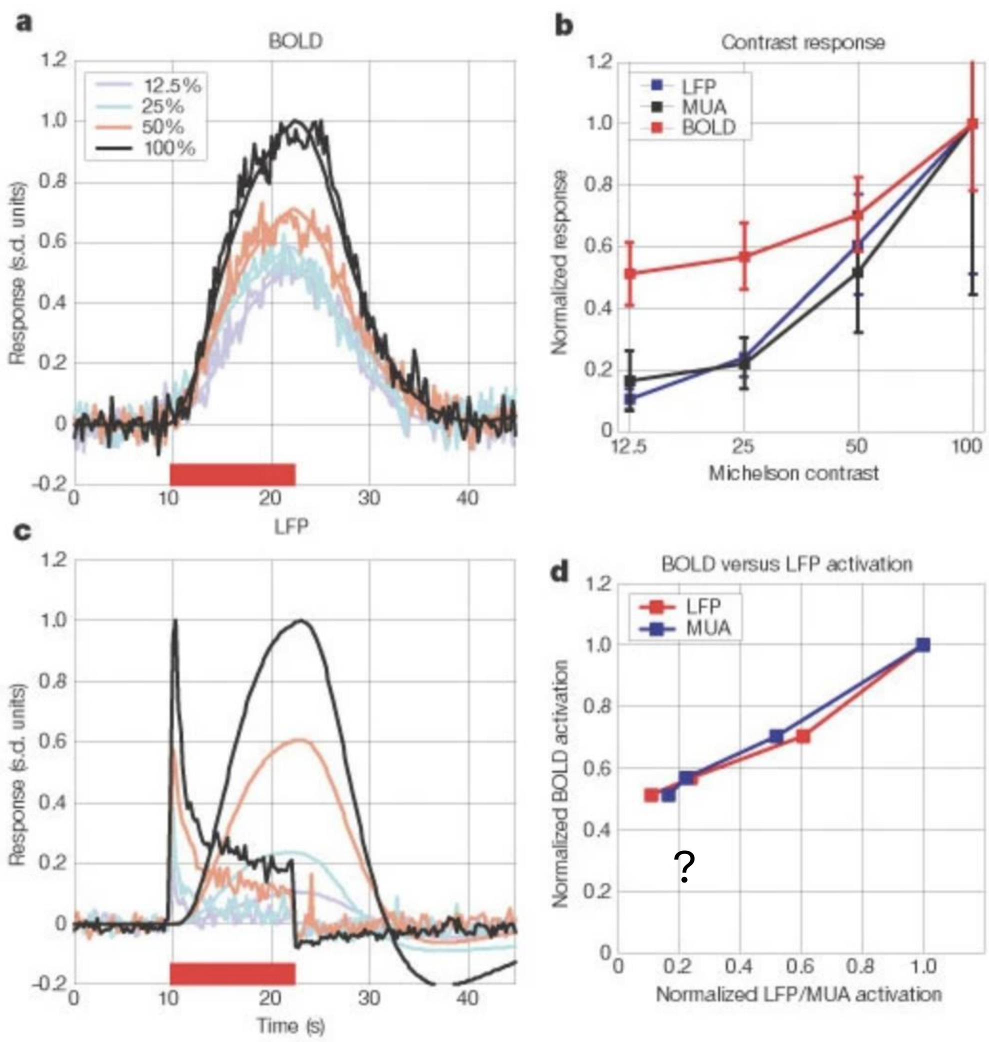
Perfusion Imaging using Arterial Spin Labelling (ASL).



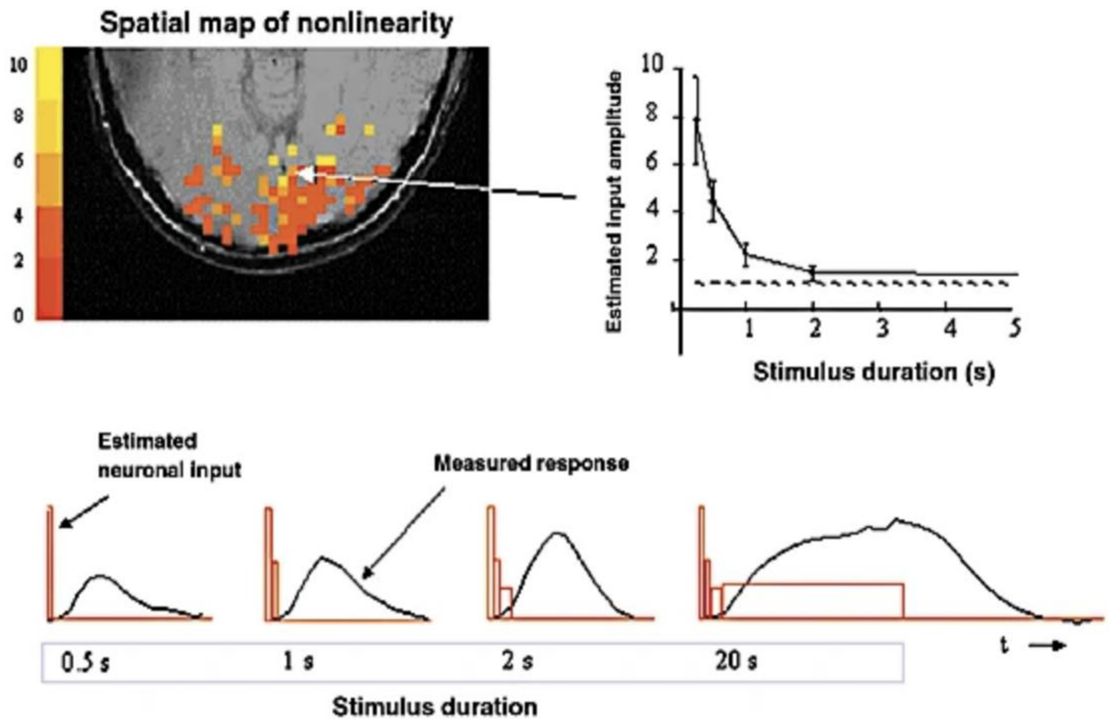


T.L. Davis, K.K. Kwong, R.M. Weisskoff, & B.R. Rosen, Calibrated functional MRI: Mapping the dynamics of oxidative metabolism, Proc. Natl. Acad. Sci. U.S.A. 95 (4) 1834-1839, https://doi.org/10.1073/pnas.95.4.1834 (1998).

We directly compared BOLD contrast with electrophysiological measures and found nonlinearities.



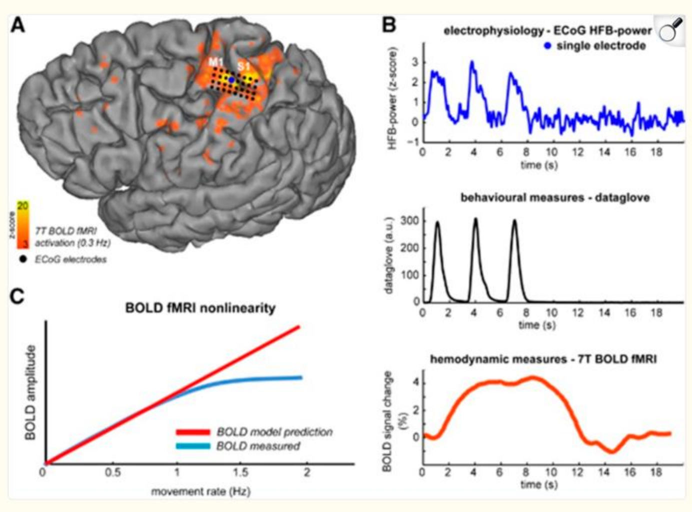
Logothetis et al, Nature 412, 150-157 (2001)

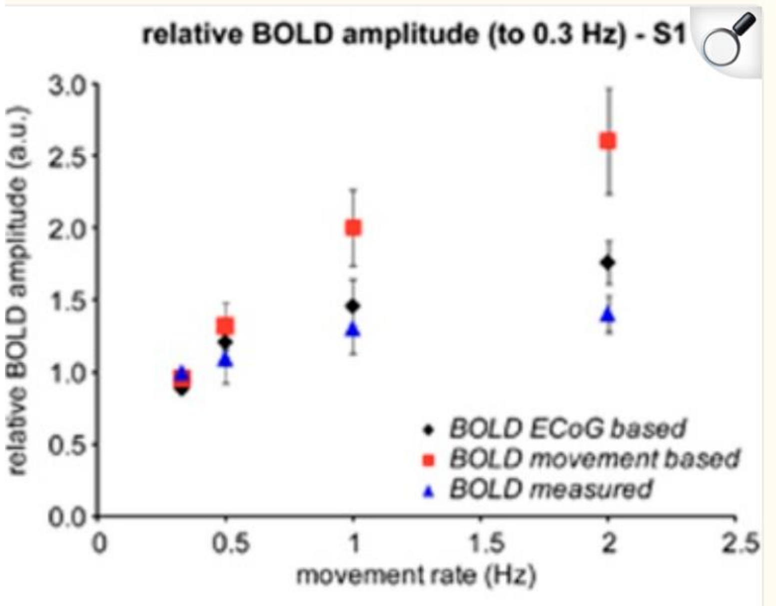


Bandettini & Ungerleider, Nature Neuroscience 4, 864-866 (2001)

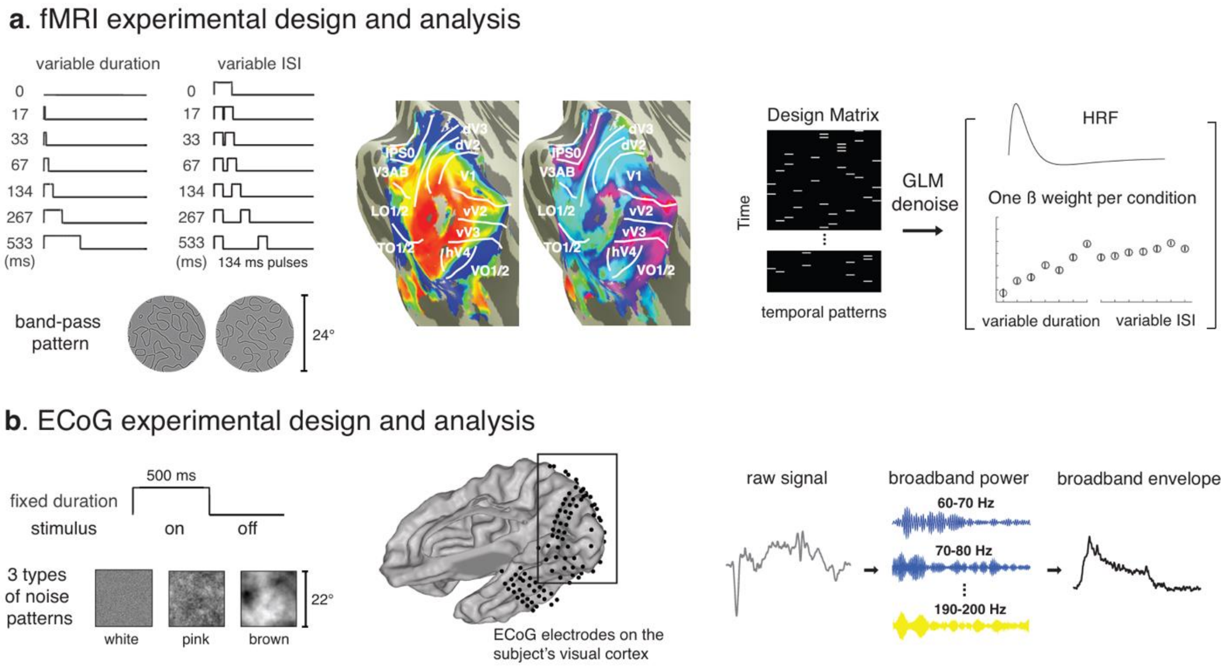
Are these nonlinearites neuronal or hemodynamic?

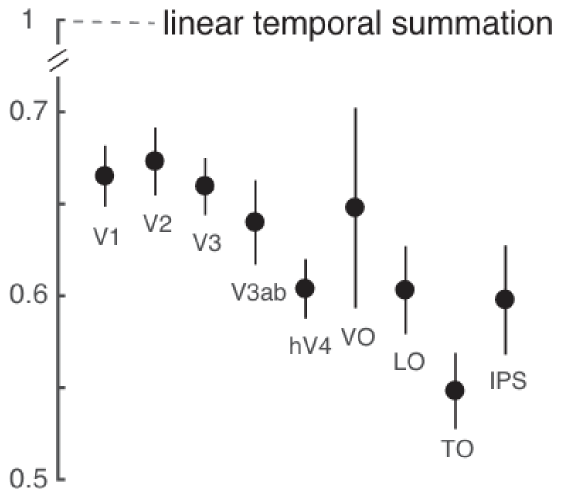
Most nonlinearities are NEURONAL…and BOLD is exquisitely sensitive.





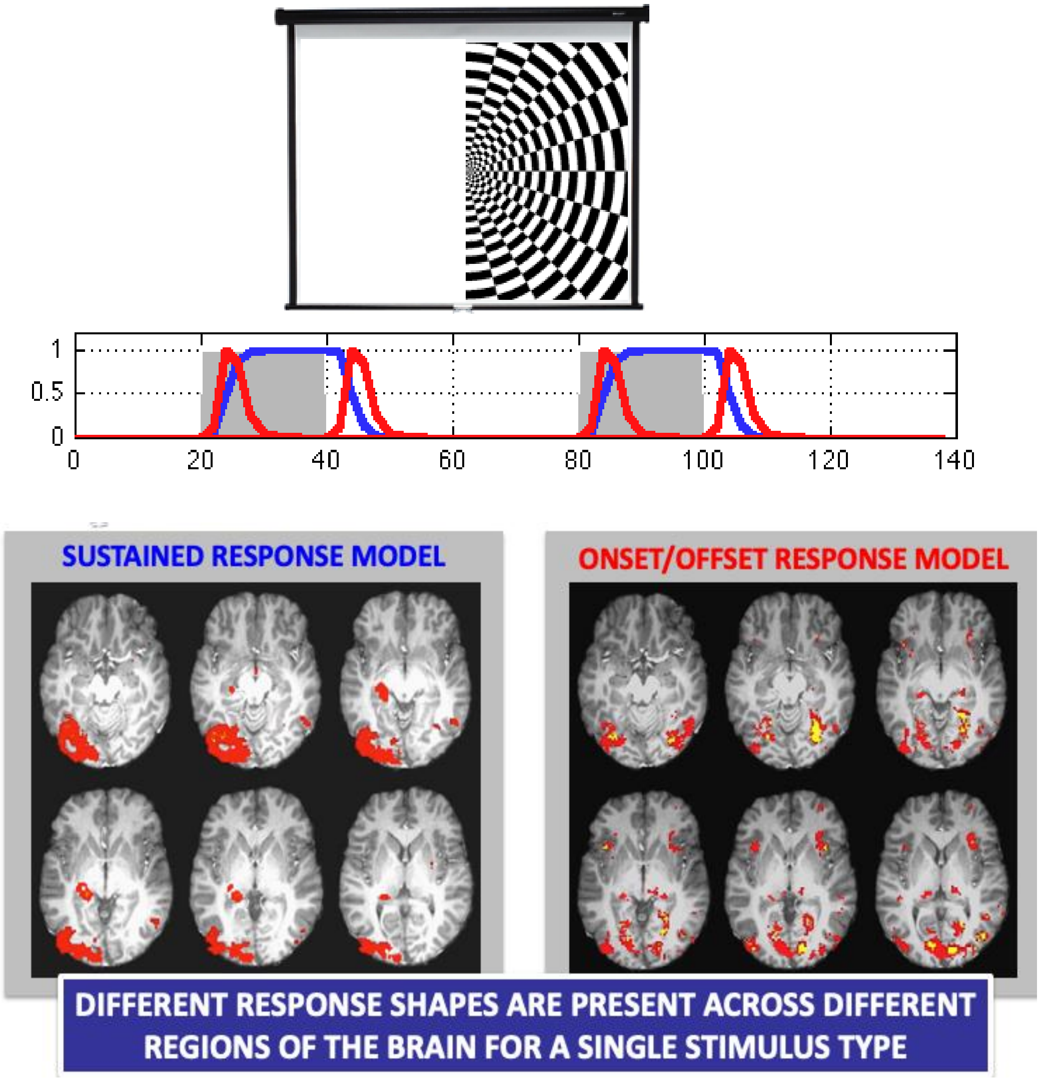
Siero JC, et al. BOLD consistently matches electrophysiology in human sensorimotor cortex at increasing movement rates: a combined 7T fMRI and ECoG study on neurovascular coupling. J Cereb Blood Flow Metab. 2013 Sep;33(9):1448-56.





Zhou, S…Modeling systematic differences in temporal summation and adaptation in human visual cortex: evidence from fMRI, BioRxiv preprint doi: https://doi.org/10.1101/108639 ;

The field began to explore beyond a single canonical neuronal function convolved with the HRF.



Uludag et al. Magn Reson Imaging, 26, 863-9 (2008).

9 Hours of Averaging with Unconstrained Model

K-means clustering of all time-locked signal

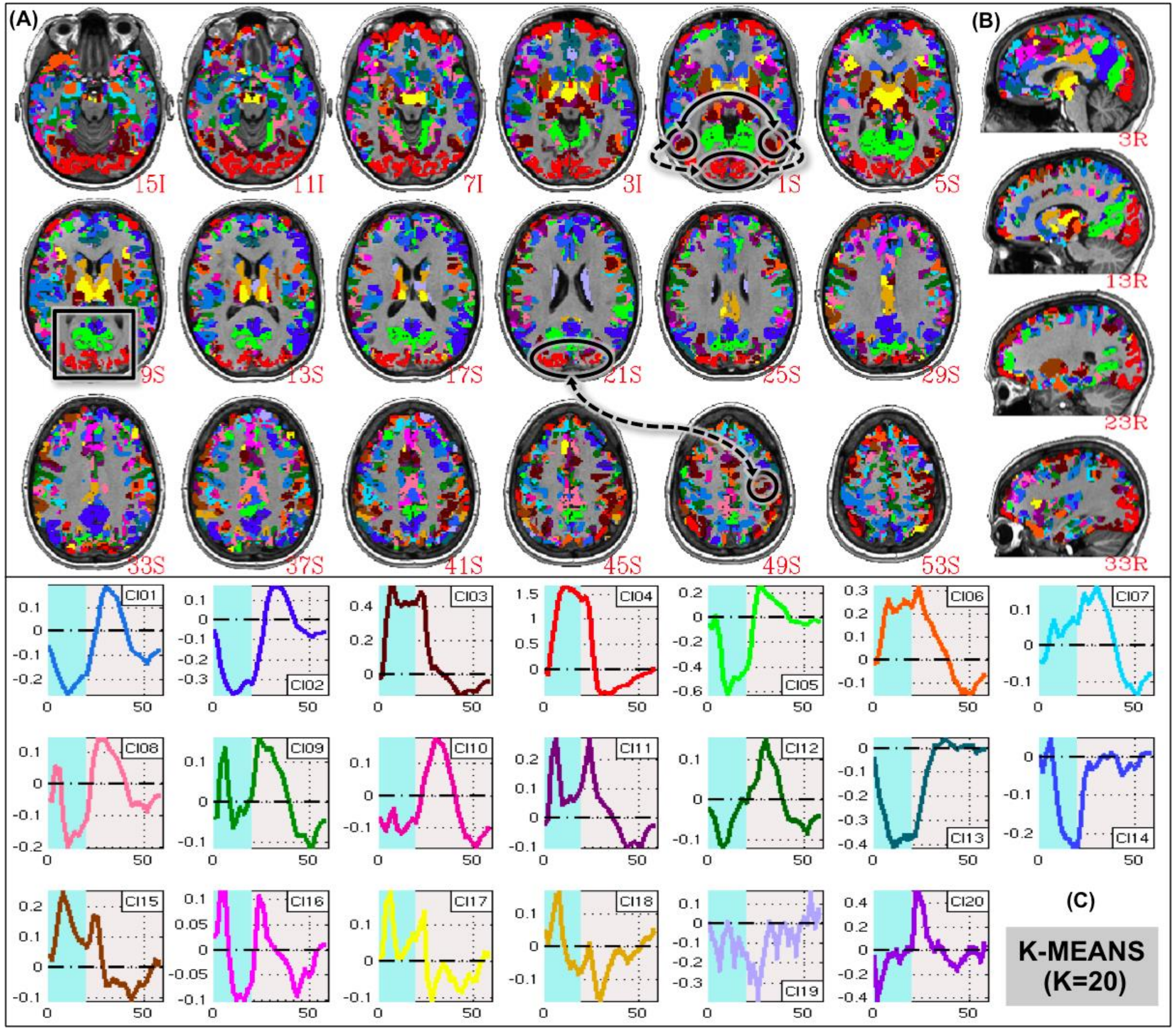
Simple full field checkerboard with word/letter discrimination task

All grey matter is activated.

The creative tension in fMRI:

Interpretability requires a model
However, any model may miss salient data.

Here, fMRI may help drive the research of other modalities, providing hypotheses of where and how to measure invasively.

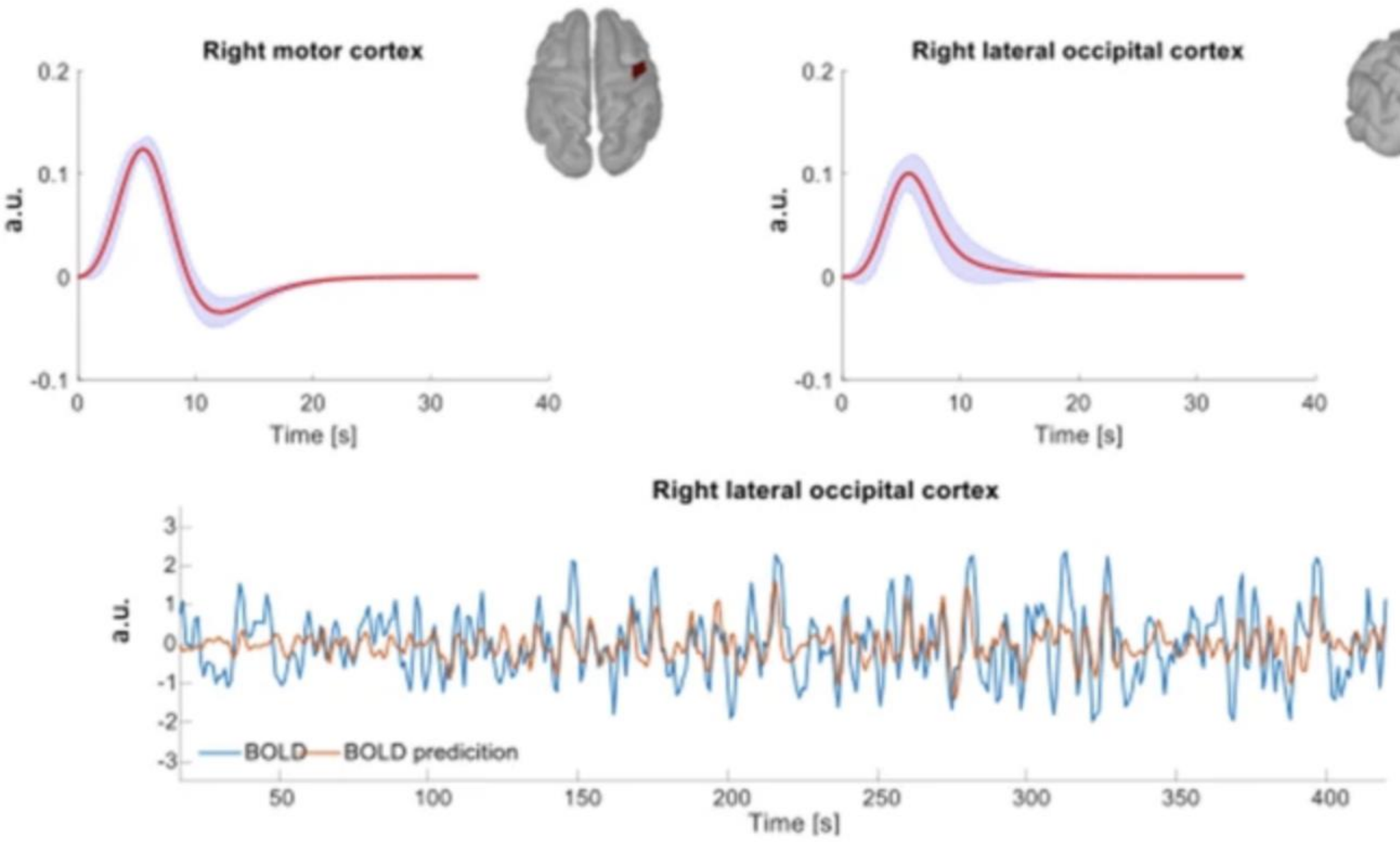


J. Gonzalez-Castillo, et al. PNAS 109, 5487-5492 (2012)

Data-driven neuronal regressor generation:
Simultaneous EEG-informed modeling of the HRF

All these features are studied and debated because:

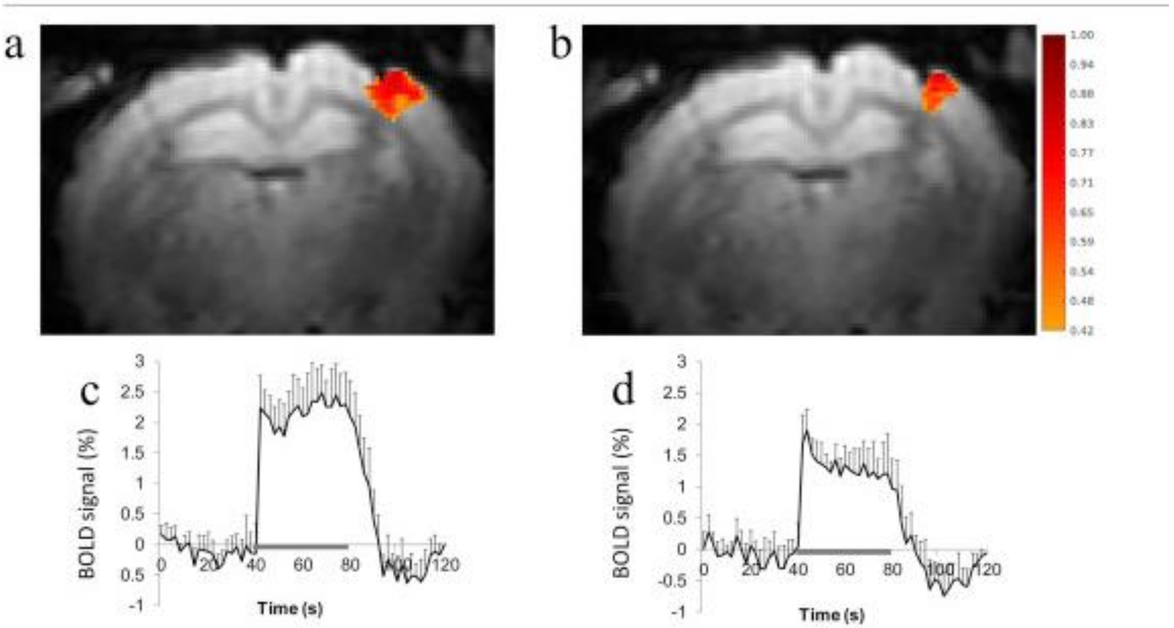
1. *Increase the transparency and utility of the signal*
2. *They might provide potential information that may be useful if understood.*



Prokopiou, P.C., Xifra-Porxas, A., Kassinopoulos, M. *et al.* Modeling the Hemodynamic Response Function Using EEG-fMRI Data During Eyes-Open Resting-State Conditions and Motor Task Execution. *Brain Topogr* **35**, 302–321 (2022).

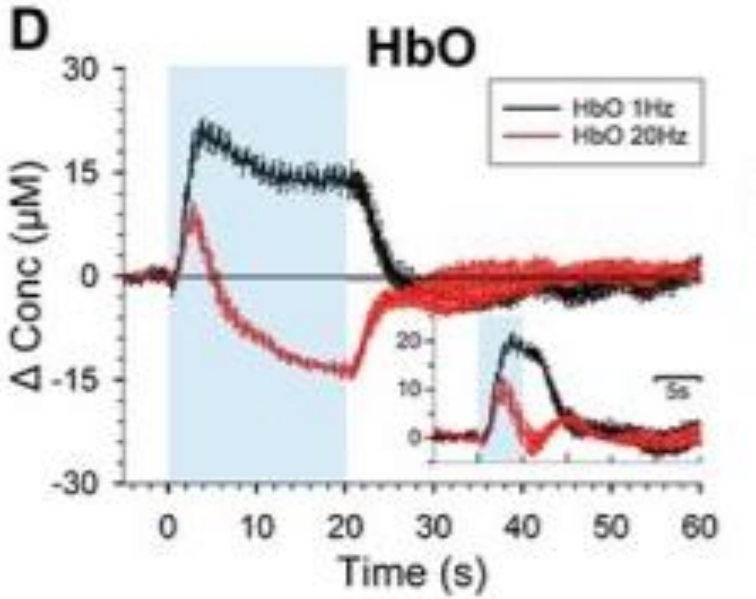
Underlying influences on BOLD contrast: Inhibition vs. excitation ...

Before and after muscimol (GABA agonist) -> increases inhibitory activity



DP Aksenov et al, NeuroImage (2019)

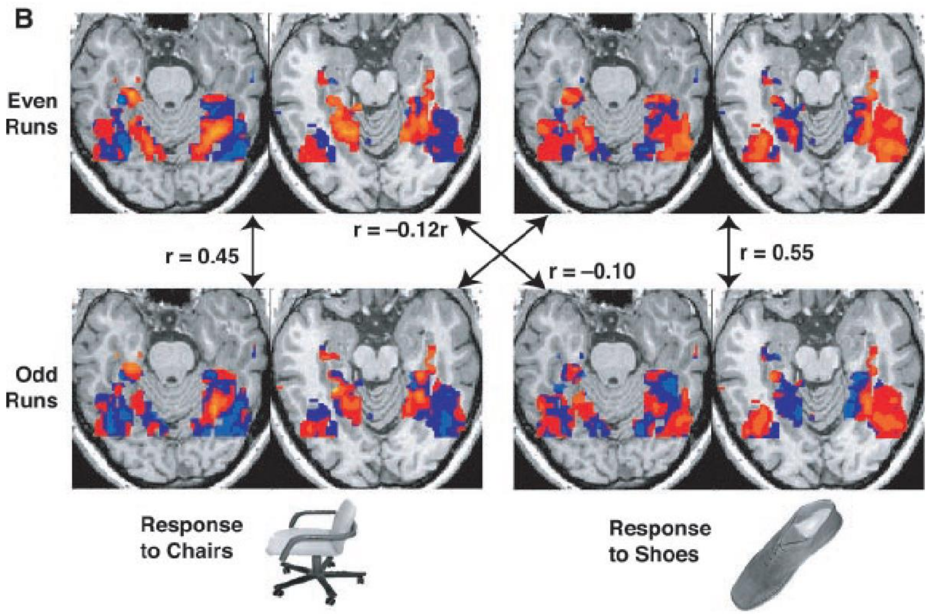
Optogentic stimulation: Excitatory and Inhibitory Neurons



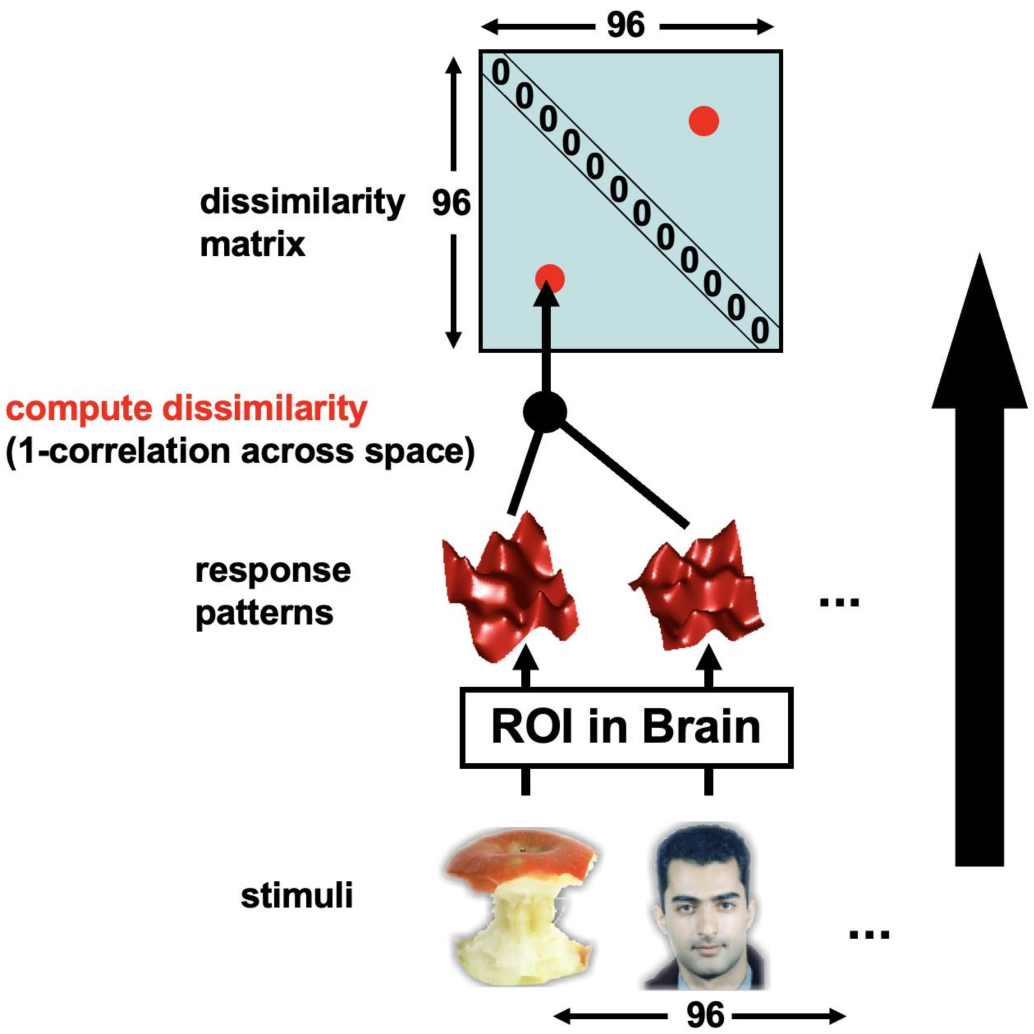
HS Moon et al, Cereb Cortex 31 (9): 4053-4067 (2021)

Increased Field Strength, RF Coil Arrays, Image Acquisition Strategies Highlighted new avenues for of fMRI

Going from Blobs to Patterns in the voxels:

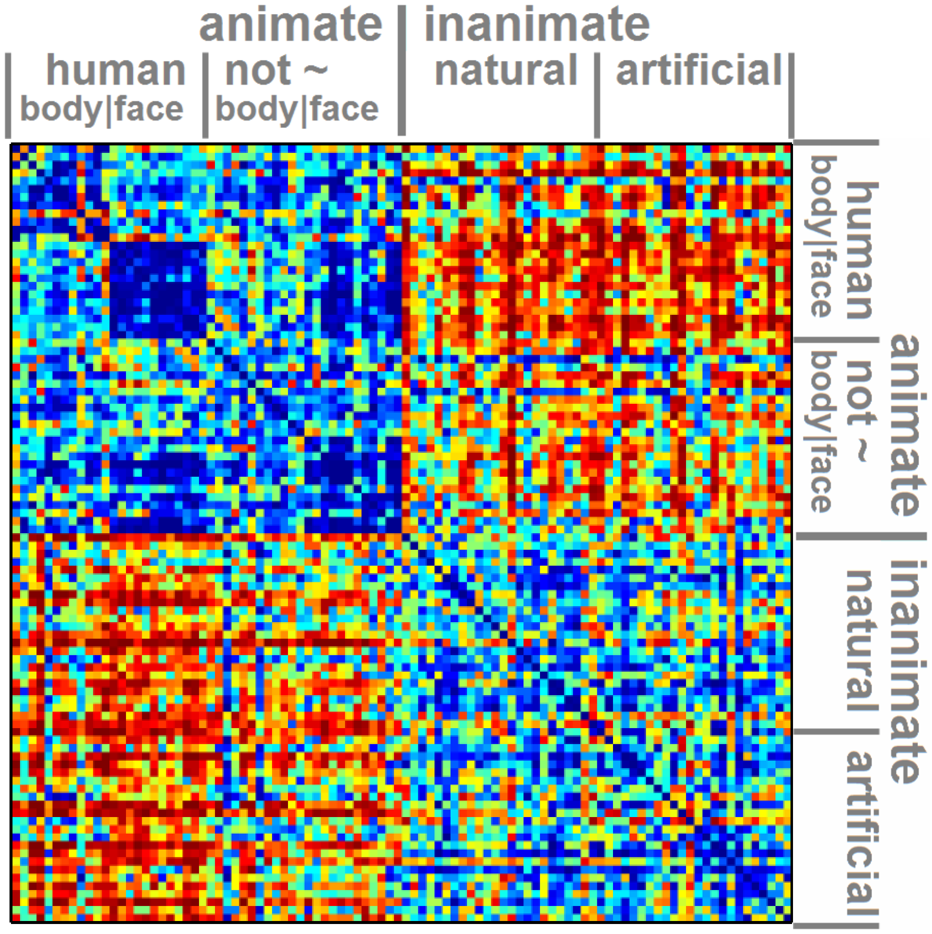


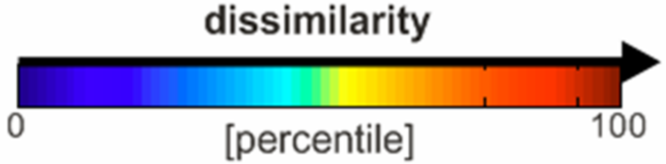
Haxby et al. Nature (2001)



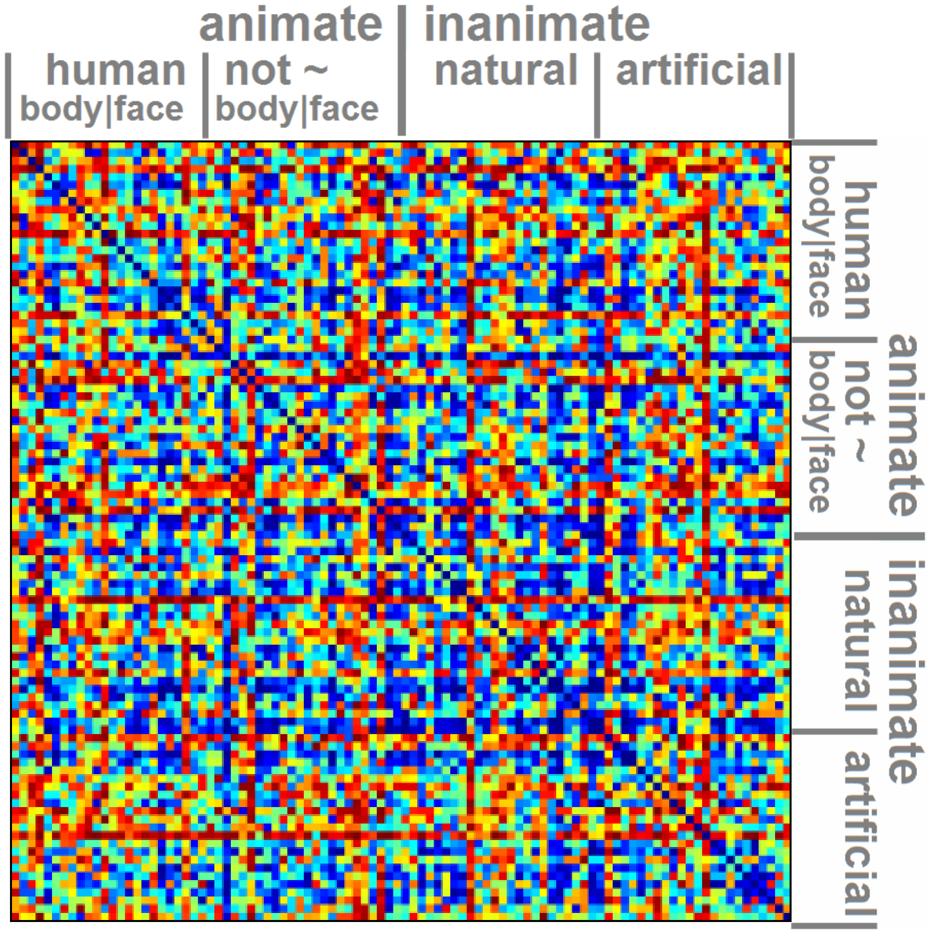
N. Kriegeskorte et al, Neuron 60, 1-16 (2008)

Human IT
(1000 visually most responsive voxels)





Human Early Visual Cortex
(1057 visually most responsive voxels)



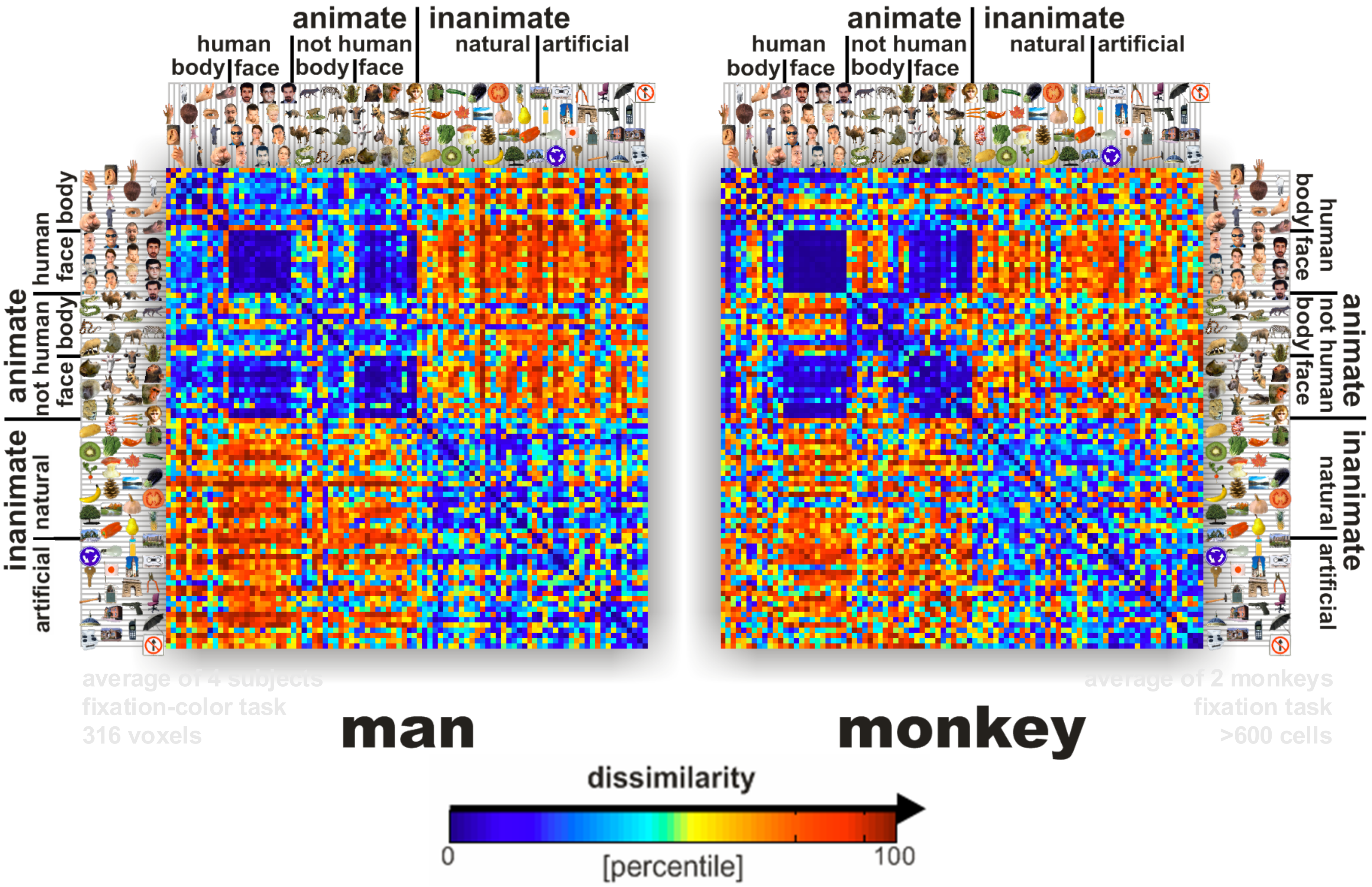
Monkey (electrode) and Human (fMRI voxel) Comparison Procedure

Human

- fMRI in four subjects
  (repeated sessions,
  >12 runs per subject)
- "quick" event-related design
  (stimulus duration: 300ms,
  stimulus onset asynchrony: 4s)
- fixation task
  (with discrimination of fixation-point color changes)
- occipitotemporal measurement slab
  (5-cm thick)
- small voxels ($1.95 \times 1.95 \times 2 mm^3$)
- 3T magnet, 16-channel coil
  (SENSE, acc. fac. 2)

Monkey (Kiani et al. 2007)

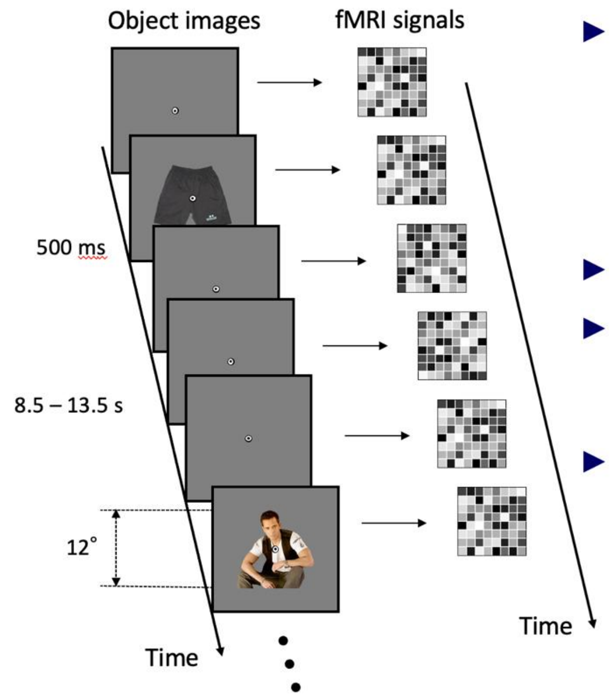
- single-cell recordings in two monkeys
- rapid serial presentation
  (stimulus duration: 105ms)
- fixation task
- electrodes in anterior IT
  (left in monkey 1, right in monkey 2)
- 674 cells total
- windowed spike count
  (140-ms window starting 71ms after stimulus onset)


animate | inanimate
human
not human
natural
artificial
body | face
body | face
average of 4 subjects
fixation-color task
316 voxels
man
monkey
average of 2 monkeys
fixation task
>600 cells
dissimilarity
0
[percentile]
100

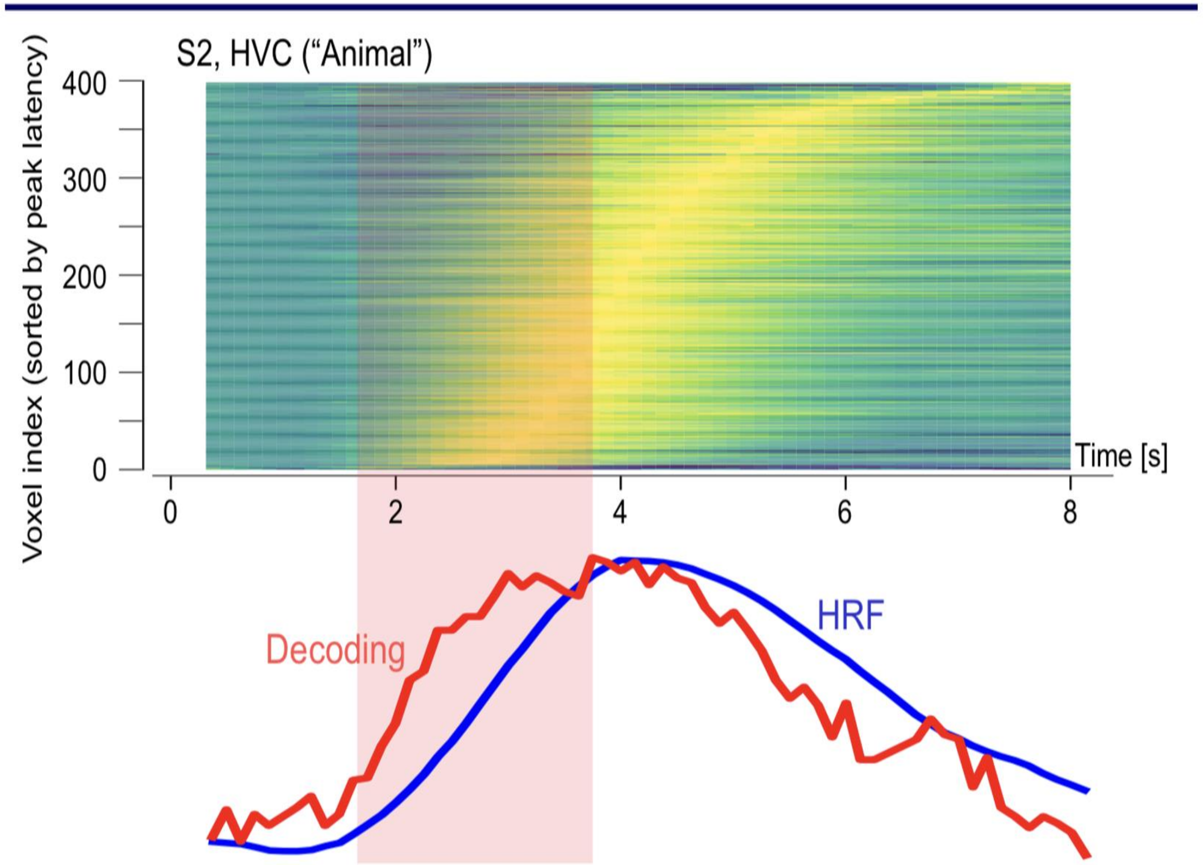
Rapid Decoding

Voxel-wise pattern information emerges with most rapid HRF responses.

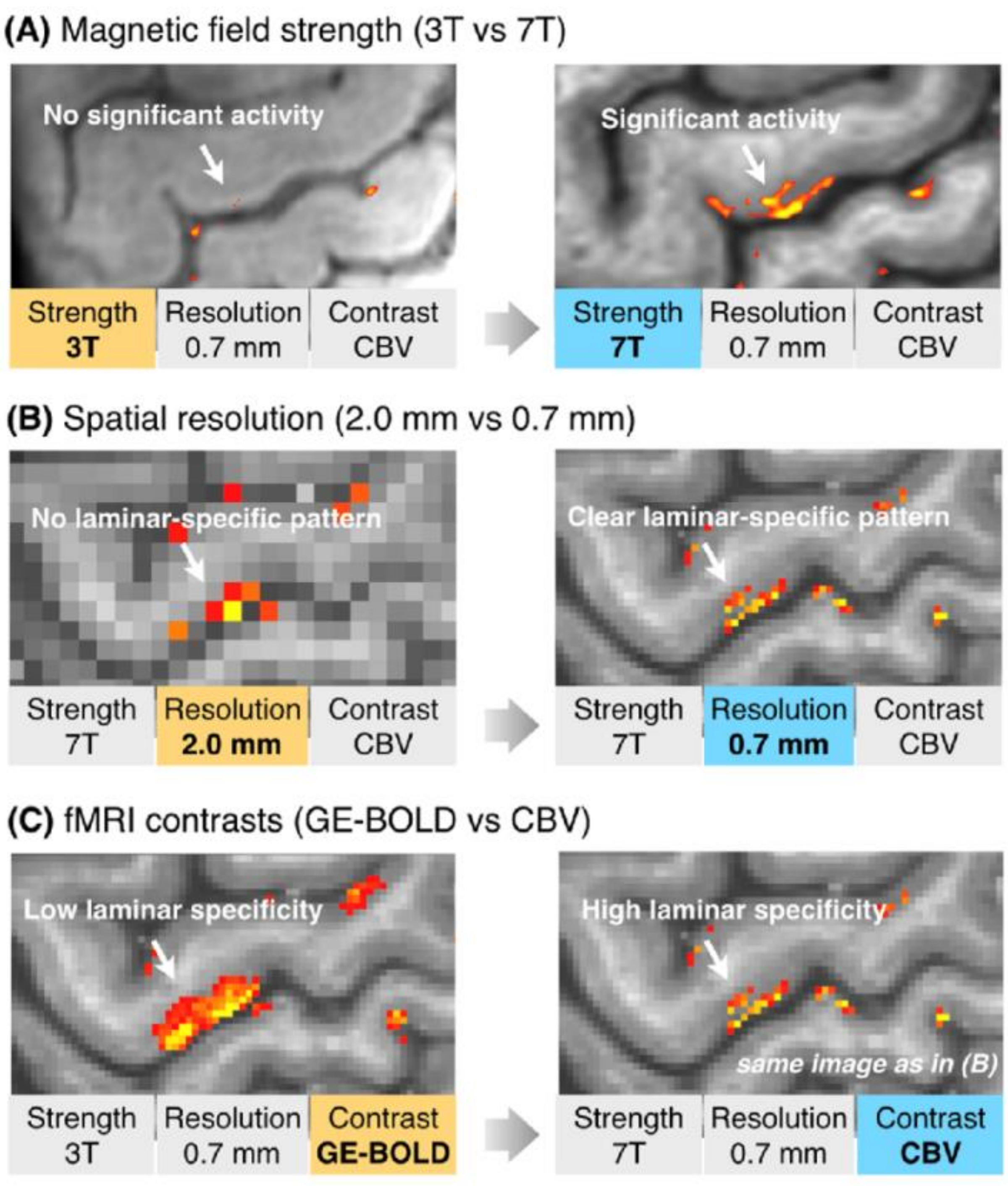
Experimental design: object image presentation



- Acquisition parameters:
  TR = 125 ms, TE = 20.8 ms, flip angle 15 deg,
  voxel size = 3 x 3 x 5 mm,
  9 slices, SMS = 3,
  3040 vols/run (~6 min)
- Subjects: N = 12
- Subject task:
  Detection of fixation color change (orthogonal task)
- Images:
  Animal (person, dog)
  Vehicle (car, airplane)

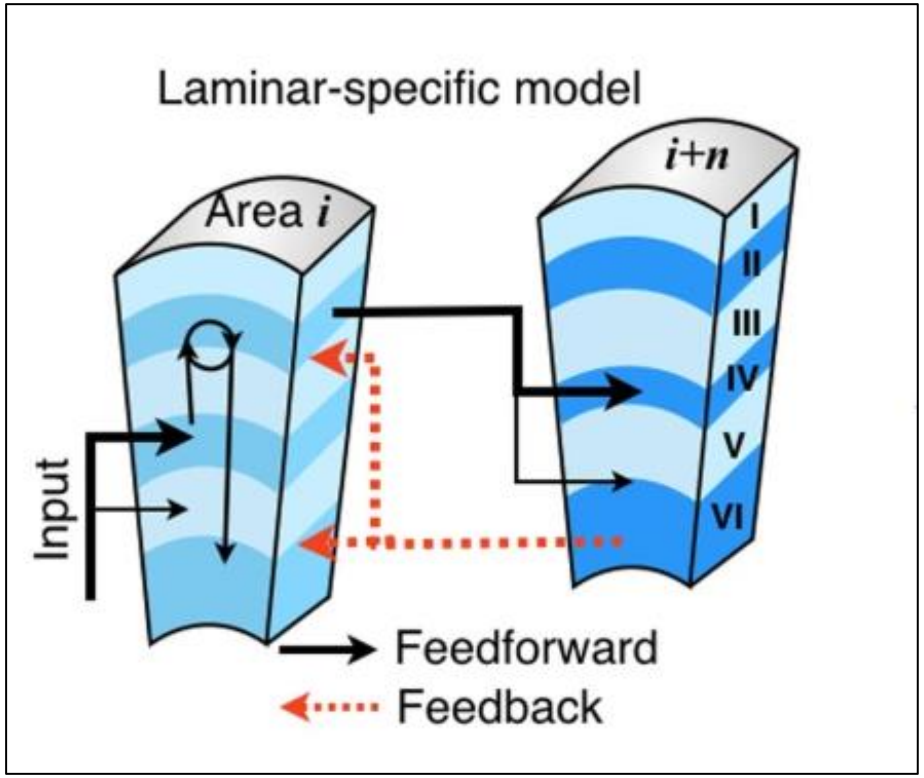


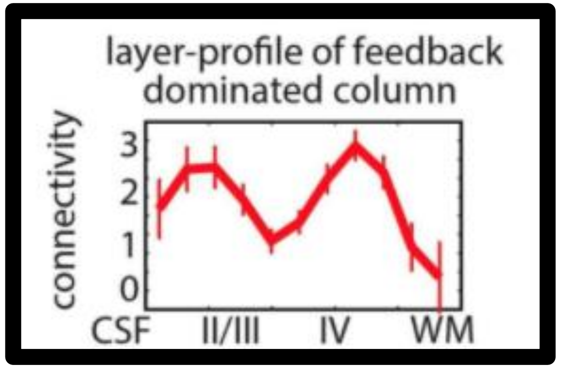
Yoichi Miyawaki, et al,**bioRxiv 2025.07.21.665938; doi: https://doi.org/10.1101/2025.07.21.665938**

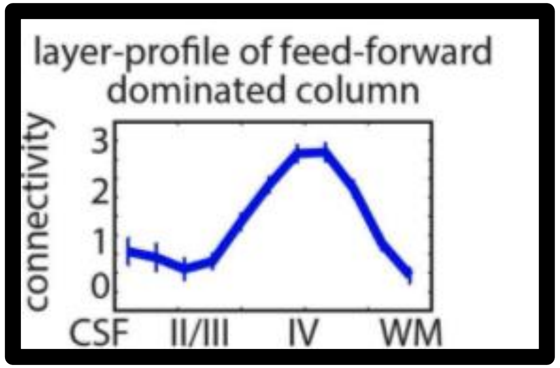


The Hope: Directional Connectivity and Functional Hierarchy

"Location" has added significance







J. Yang, et al. Neuroscience & Behavioral Reviews 2021

What contributes to spontaneous fluctuations?

Anastasia Dimakou, Giovanni Pezzulo, Andrea Zangrossi, Maurizio Corbetta, The predictive nature of spontaneous brain activity across scales and species, Neuron, Volume 113, Issue 9, 2025, Pages 1310-1332,

Spontaneous Neuronal Activity
- -arousal
- -conscious thought
- -unconscious processes

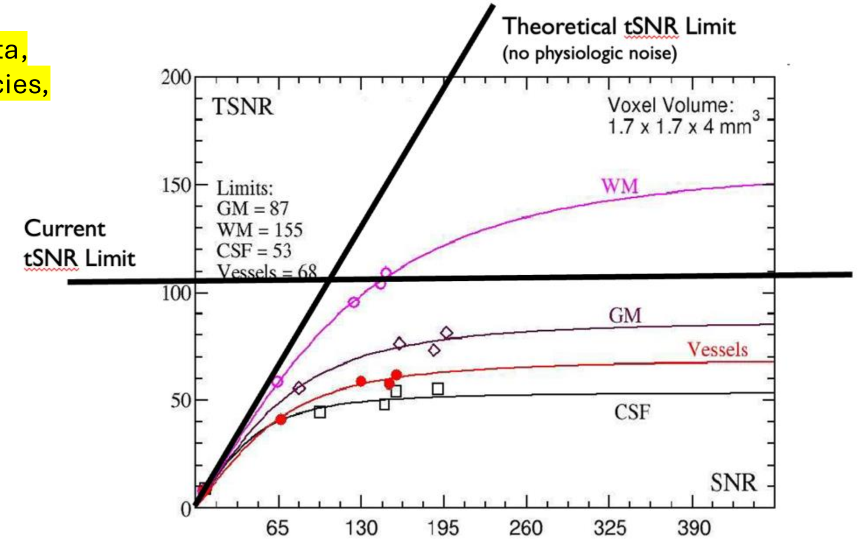
Respiration
- -chest wall B_0
- -variable end tidal CO_2 related flow/BOLD changes

Cardiac Pulsation

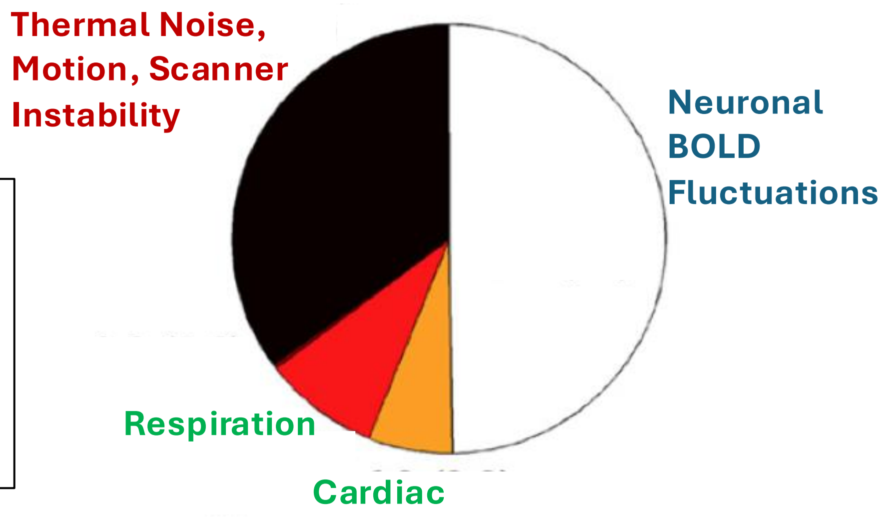
Thermal Noise
Motion
Scanner Instability

We don't understand most of these well enough.

We also don't understand the noise well enough to adequately remove it.



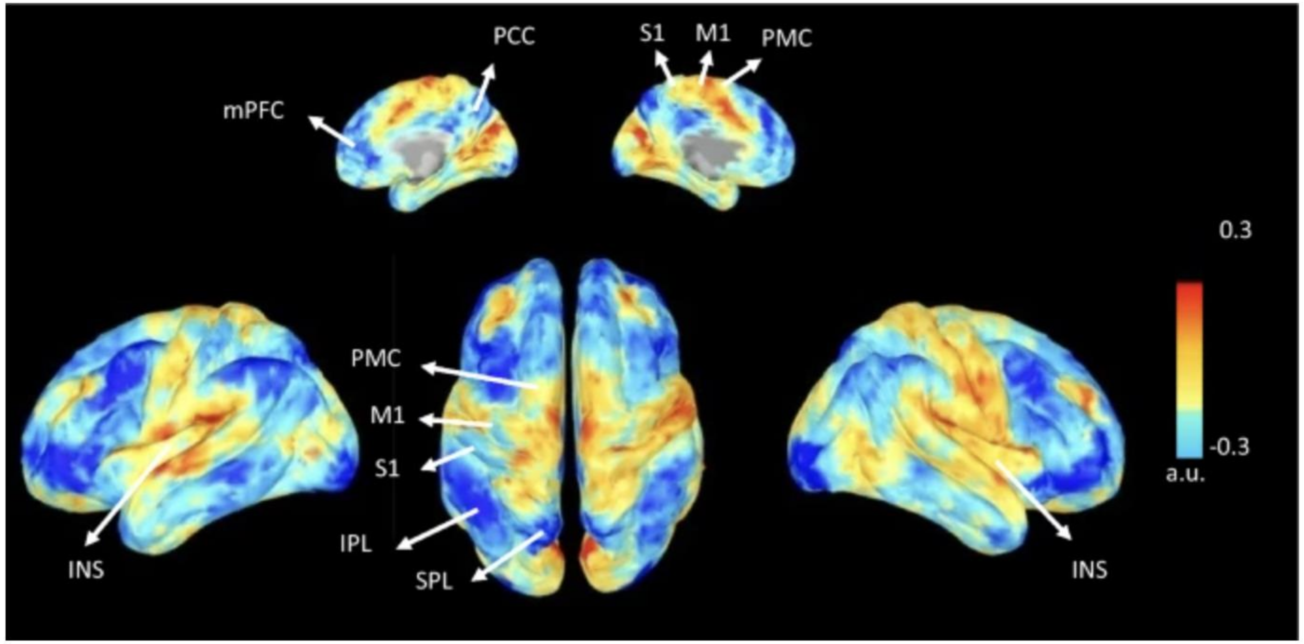
J. Bodurka et al. NeuroImage 2007



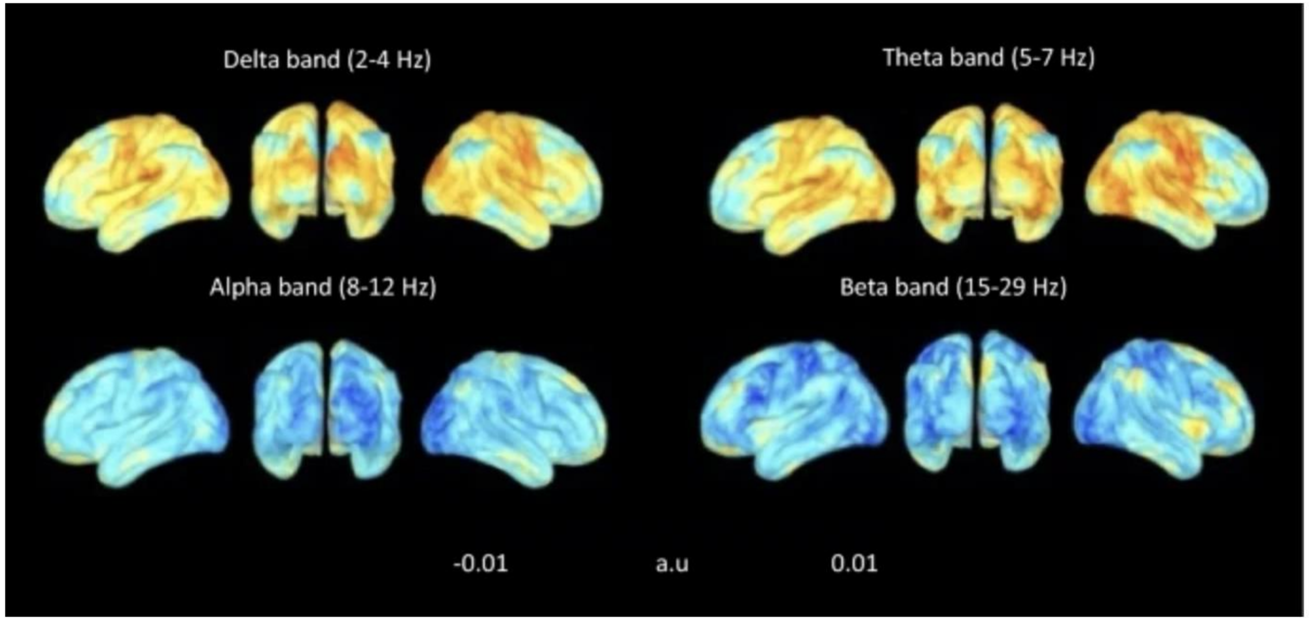
Bianciardi et al. MRI 27: 1019-1029, 2009

Positive-Negative Functional Gradients Revealed by correlations with Broadband EEG.

Resting state EEG Broadband Correlation with BOLD



Resting state EEG Band-Specific Correlation with BOLD



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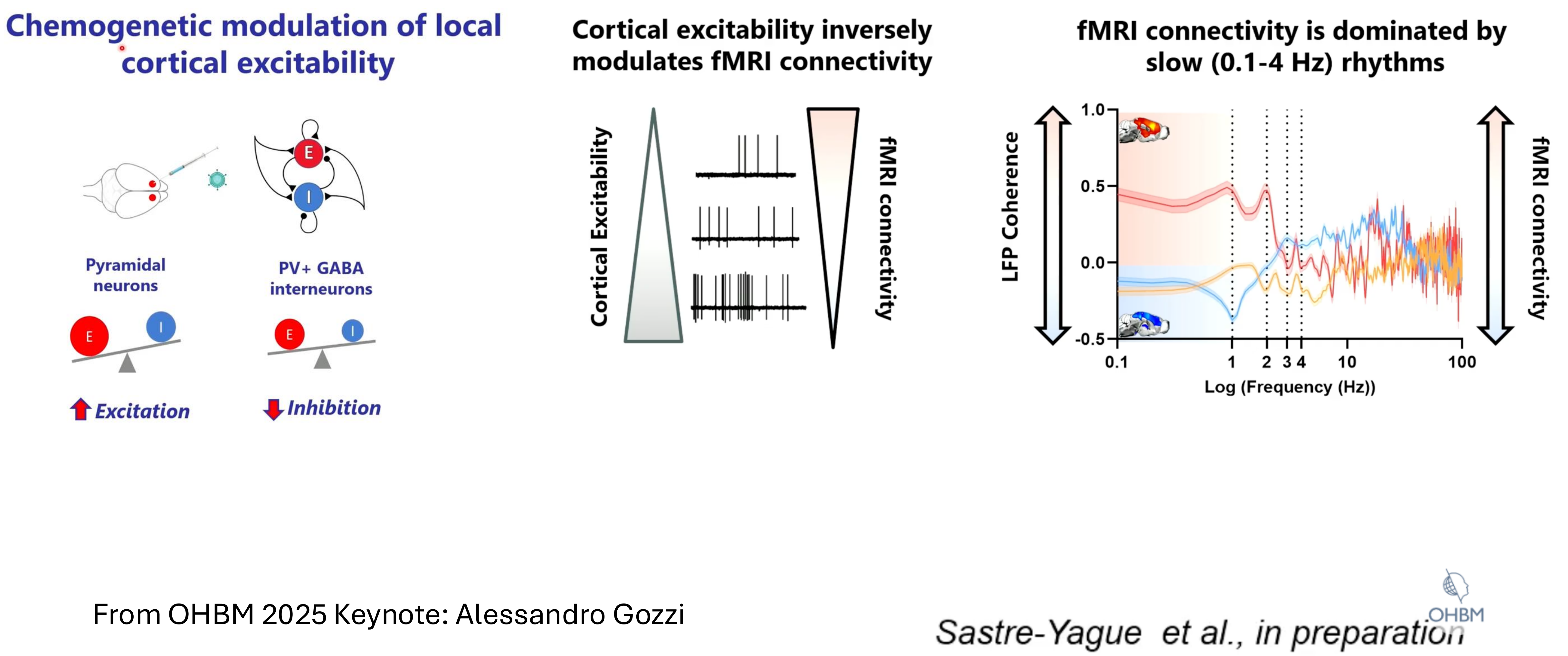


From OHBM 2025 Keynote: Alessandro Gozzi

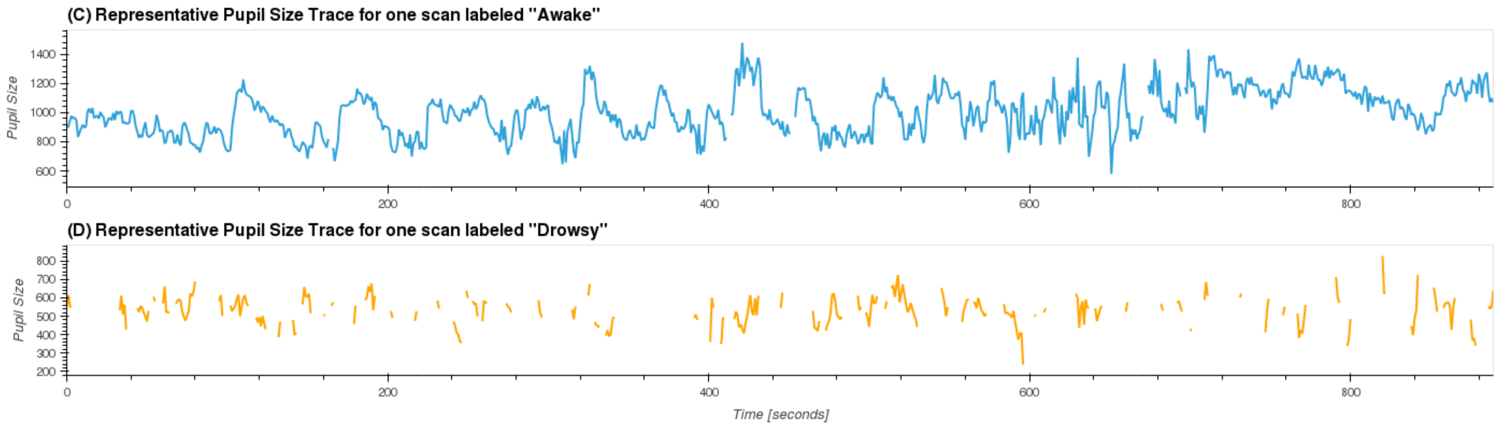
YouTube / OHBM 2925 / Keynote / Alessandro Gozzi

The effects of arousal on fluctuations.

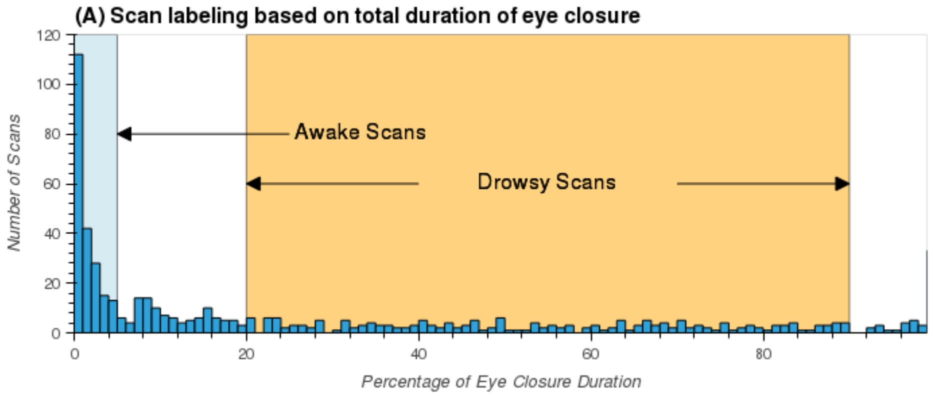
Pupil Size & Eyelid state

Awake

Drowsy



Javier Gonzalez-Castillo

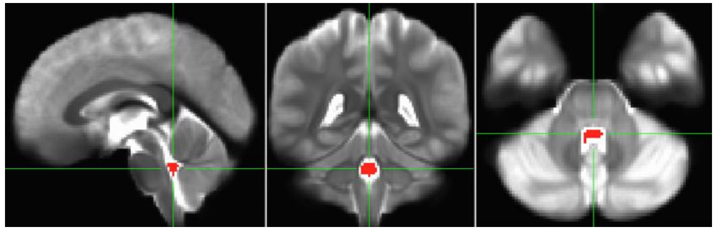


"Awake" scans: defined as those for which pupil size traces indicate subjects had their eyes closed less than 5% of the scan duration.

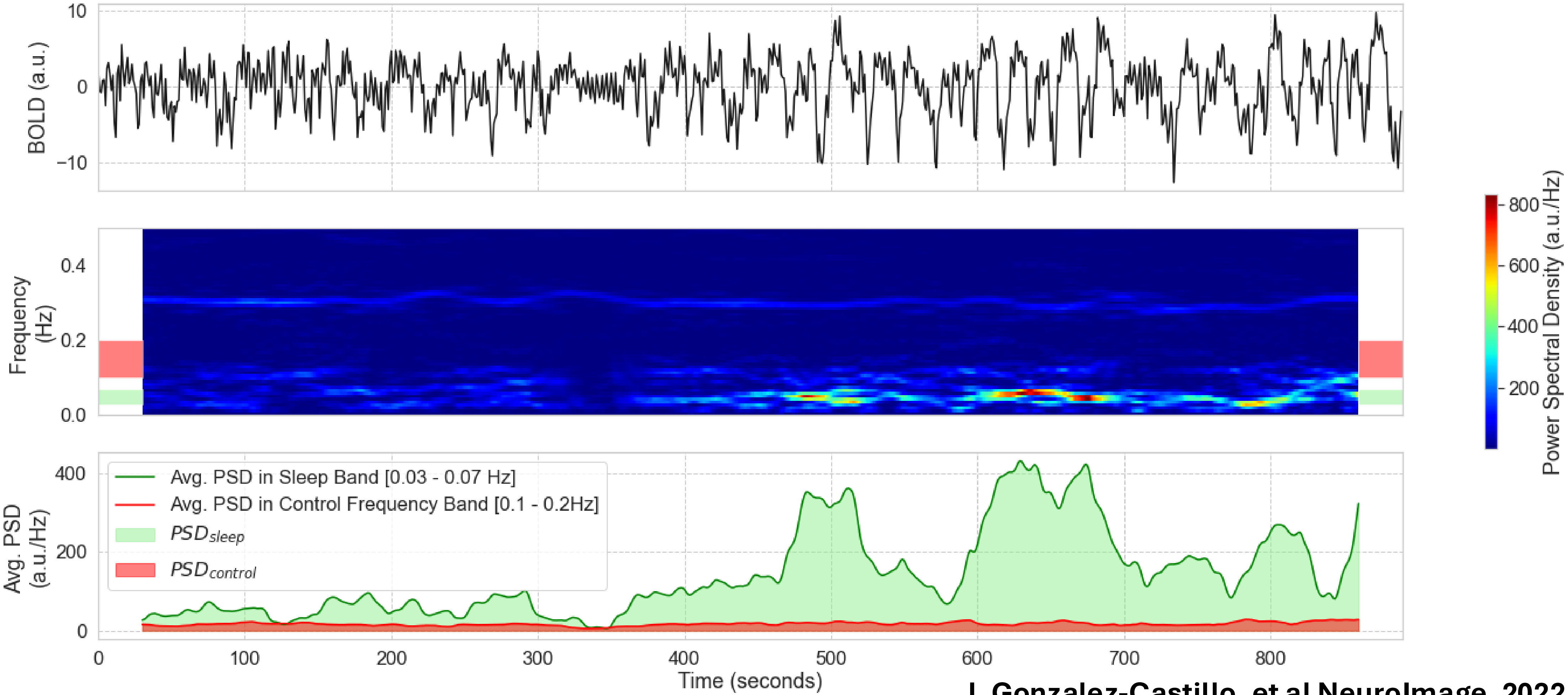
"Drowsy" scans: defined as those for which pupil size traces indicate subjects had their eyes closed between 20% and 90% of the scan duration.

- 404 scans HCP 7T Resting-state sample
- Concurrent Eye Tracking available
- Label scans as awake or drowsy

J. Gonzalez-Castillo, et al NeuroImage, 2022

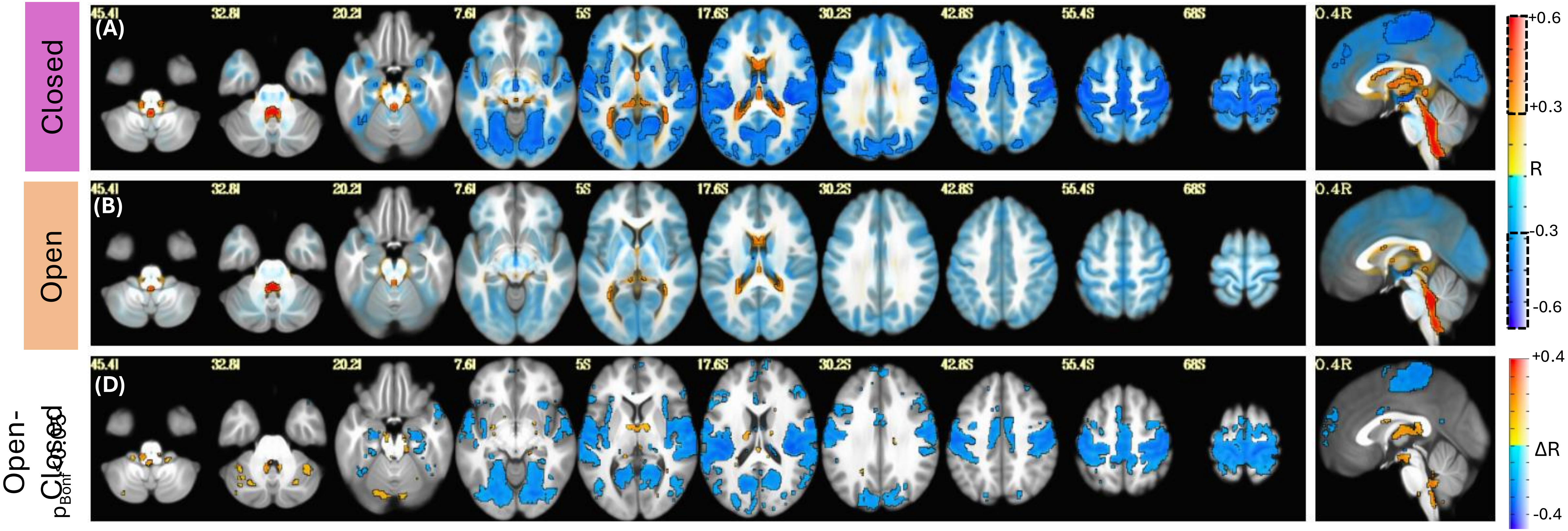


Power around 0.05 Hz in 4th Ventricle (CSF)



J. Gonzalez-Castillo, et al NeuroImage, 2022

Fluctuations Eyes Open (awake) vs Eyes Closed (sleep)

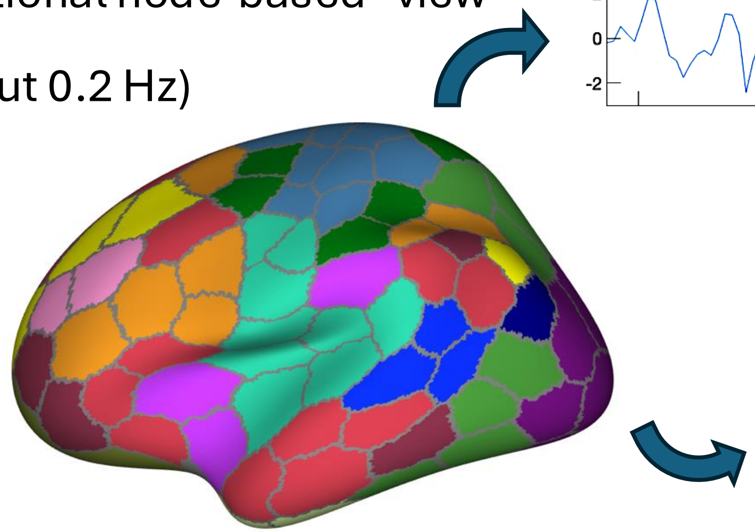


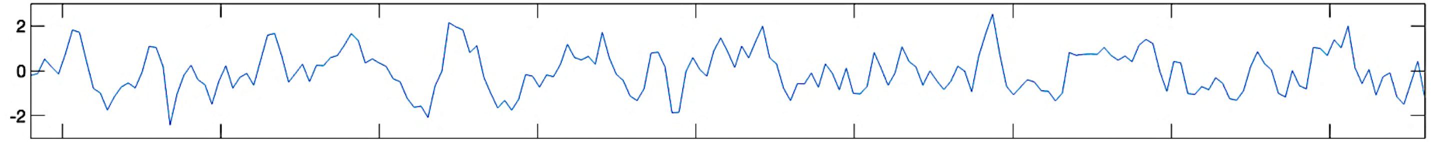
J. Gonzalez-Castillo, et al NeuroImage, 2022

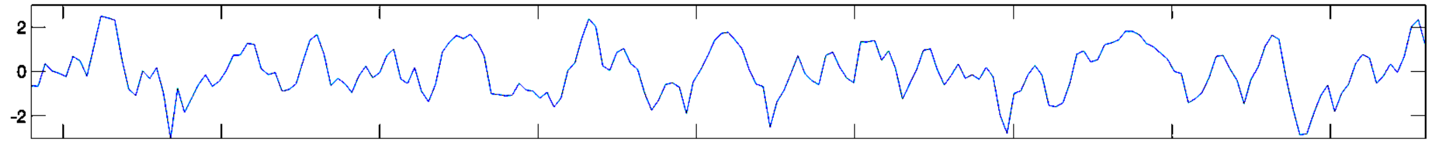
Addressing Resting State with Edge Analysis: Rethinking “0.2Hz”

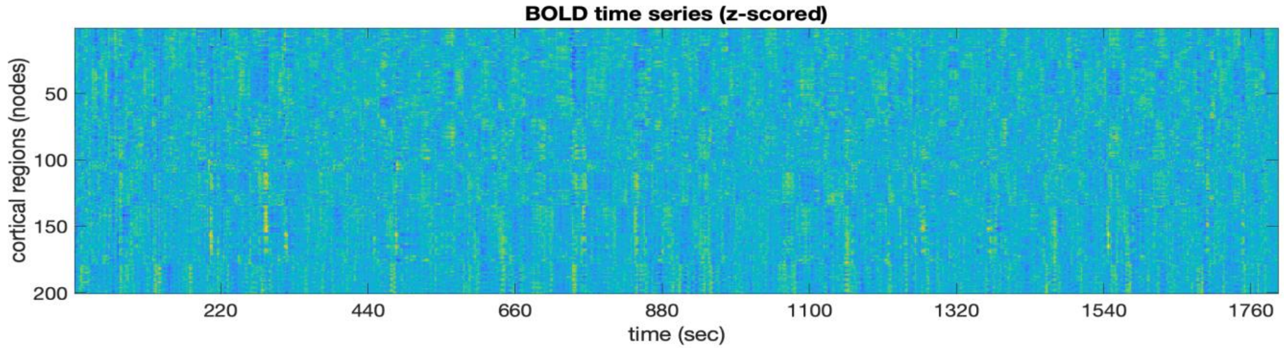
Traditional node-based “view”

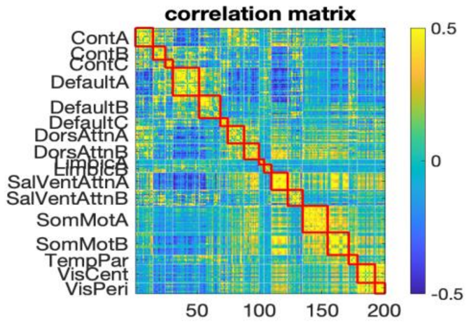
(about 0.2 Hz)

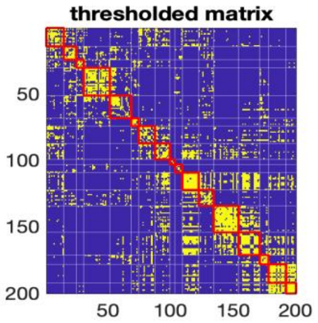






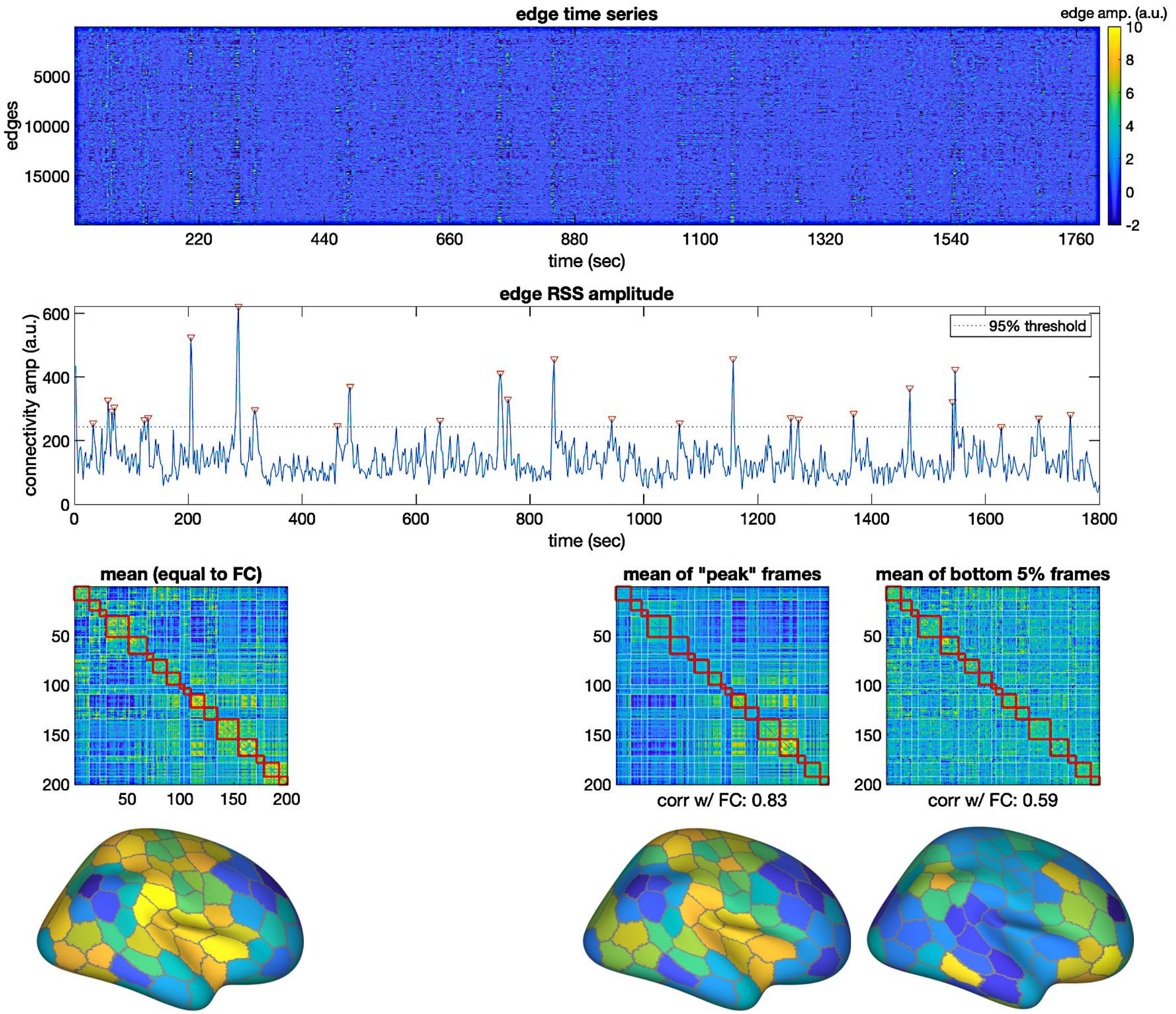






Typical time series analysis:

- Calculate the correlation matrix by taking the correlation between node pairs, forming a connectivity matrix of time-averaged similarities
- Threshold this matrix, to preform graph-theory analyses…etc..

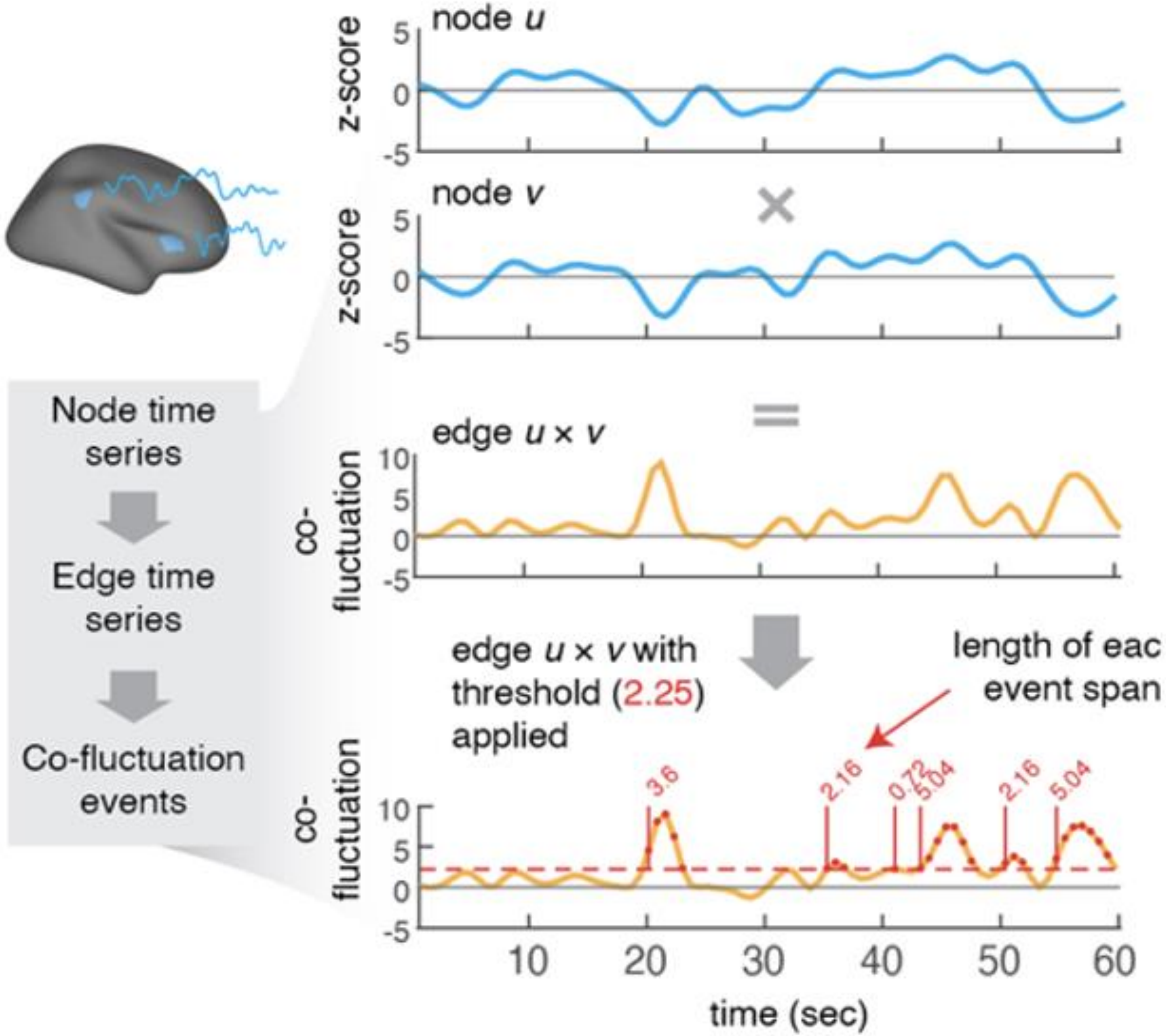


By taking the instantaneous similarity in a small fraction of the timepoints **(about 3%),** we can reconstruct broad-scale FC organization

Suggesting that FC organization is expressed in punctate events

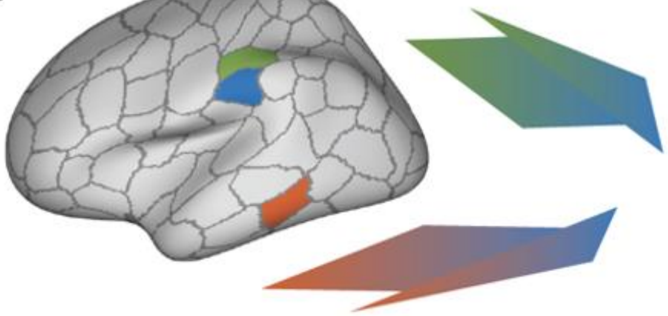
Edge Analysis and Event Duration Mapping

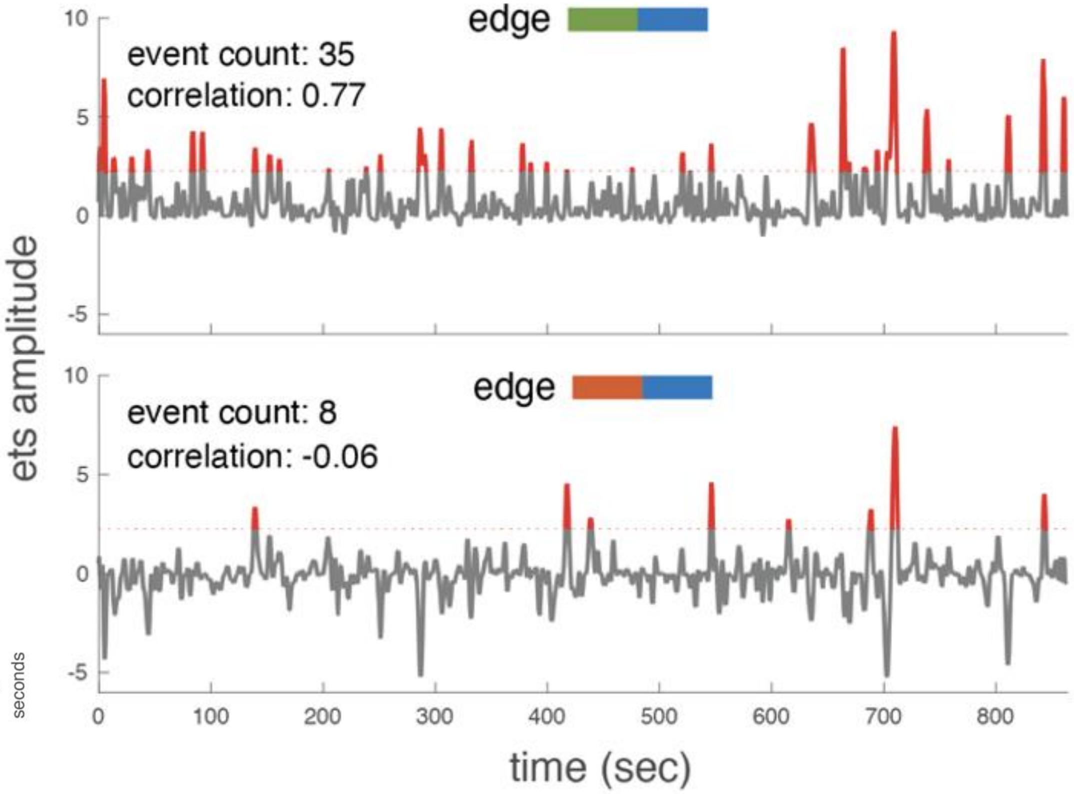
- **Resting state fMRI (0.2 Hz) is *NOT oscillatory***
- **Characterized by a series of correlated “events.”**
- **These events have different durations.**
- **The predominance of specific event durations shows spatial structure.**

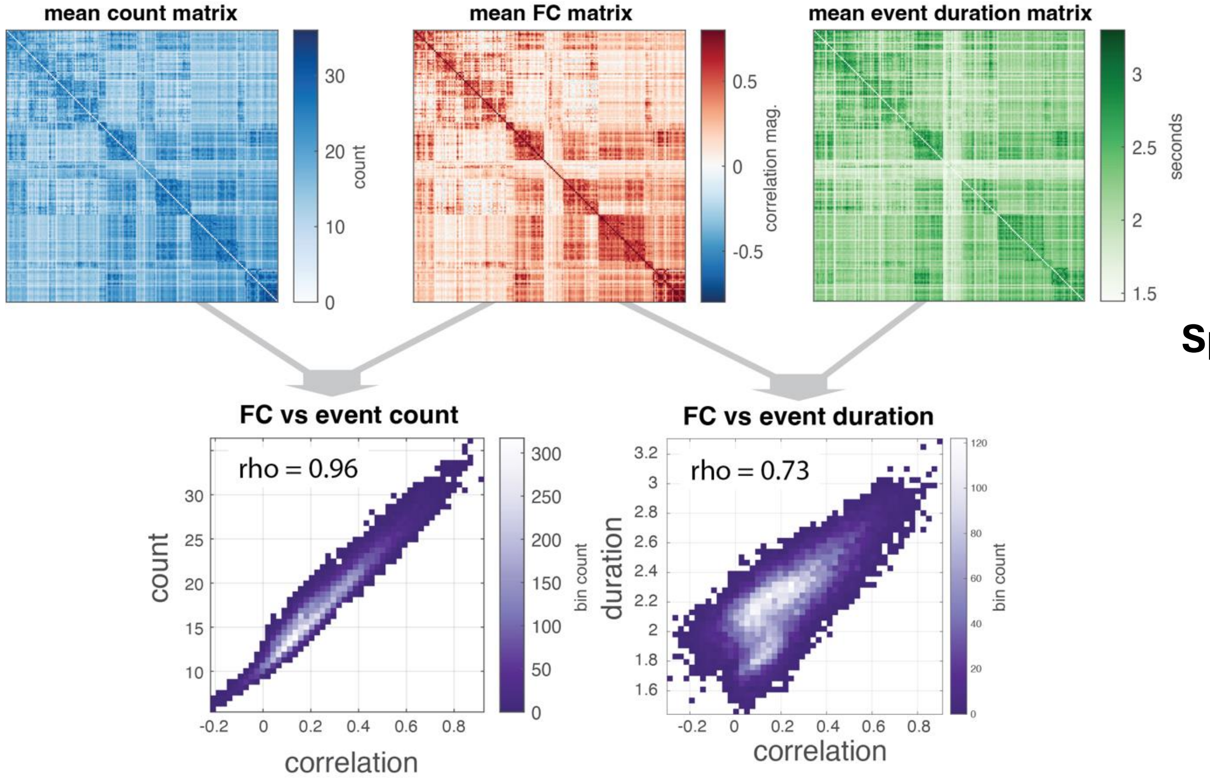


J. Faskowitz, et al. Mapping high-amplitude fMRI edge time series events across space and time, Imaging Neuroscience, In Press

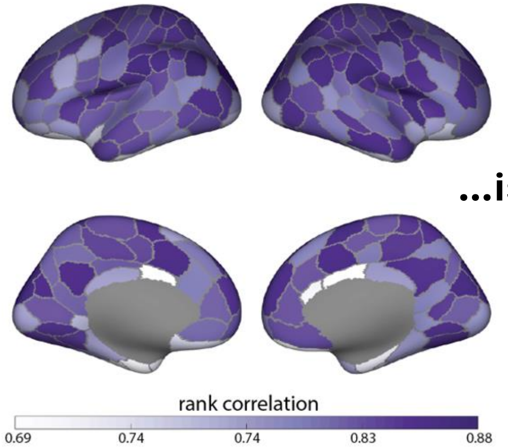
What do the edge time series look like for high vs. low correlation edges?







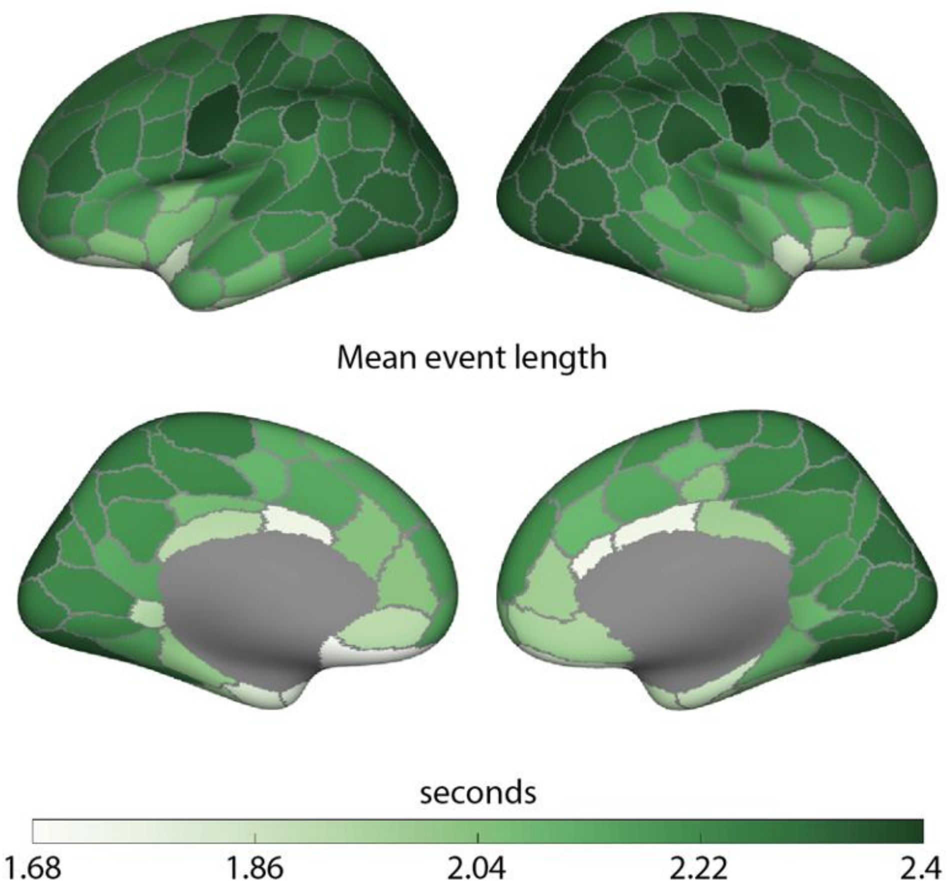
Spatial relationship between count and FC (shows heterogeneity)



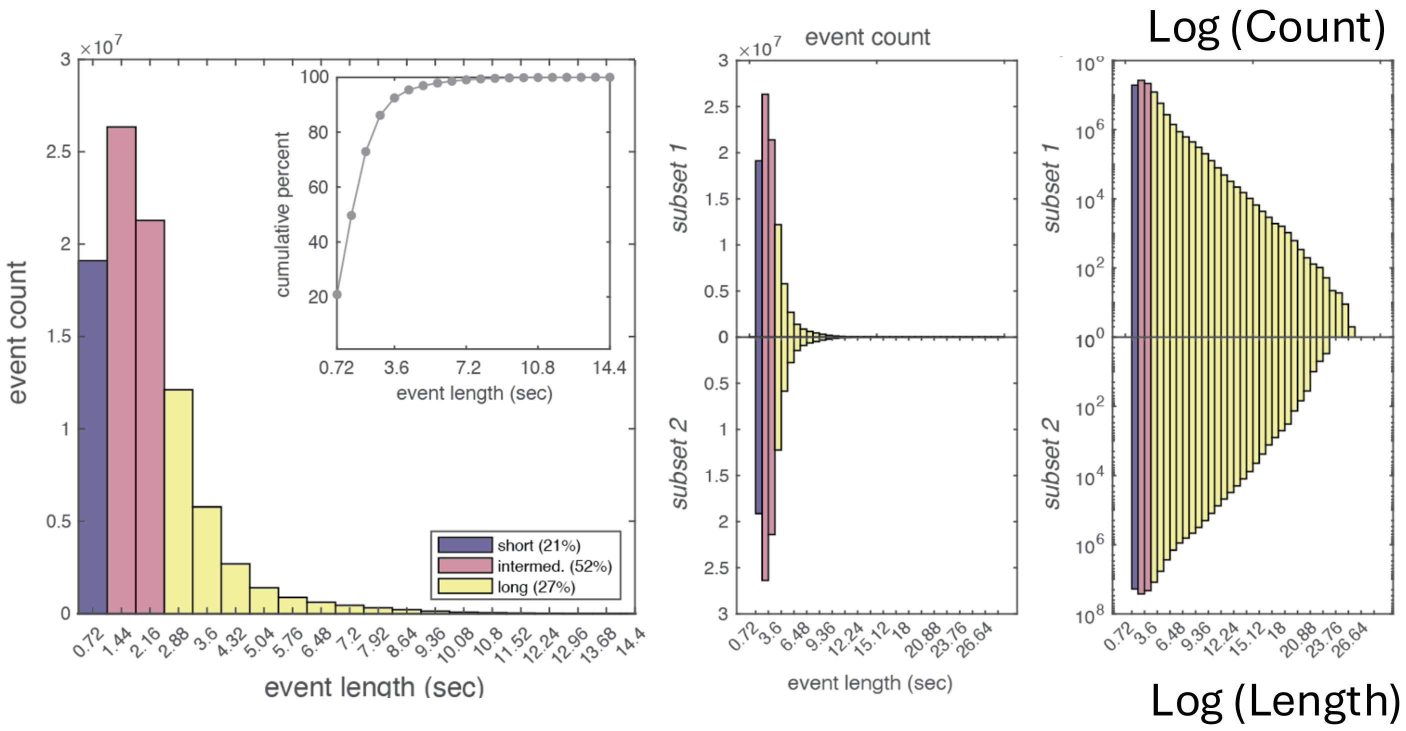
...is duration the latent variable?

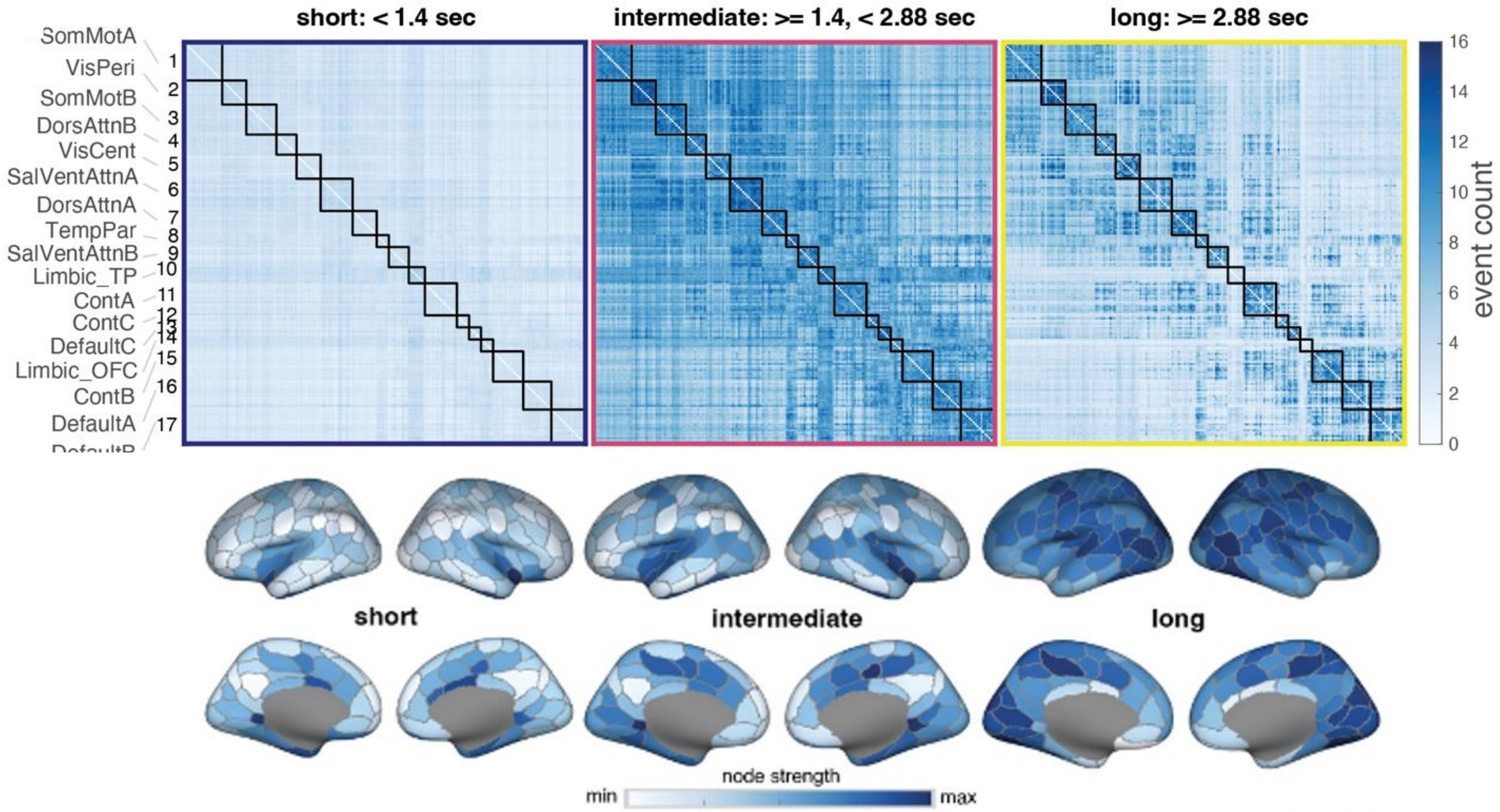
Is there added information in event duration?

Mean Event Duration Shows Spatial Structure



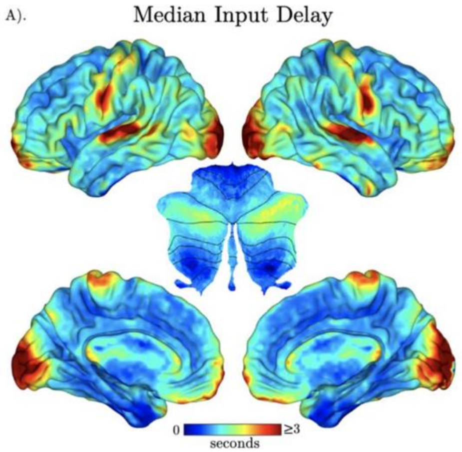
Logarithmic Distribution of Event Lengths and Counts

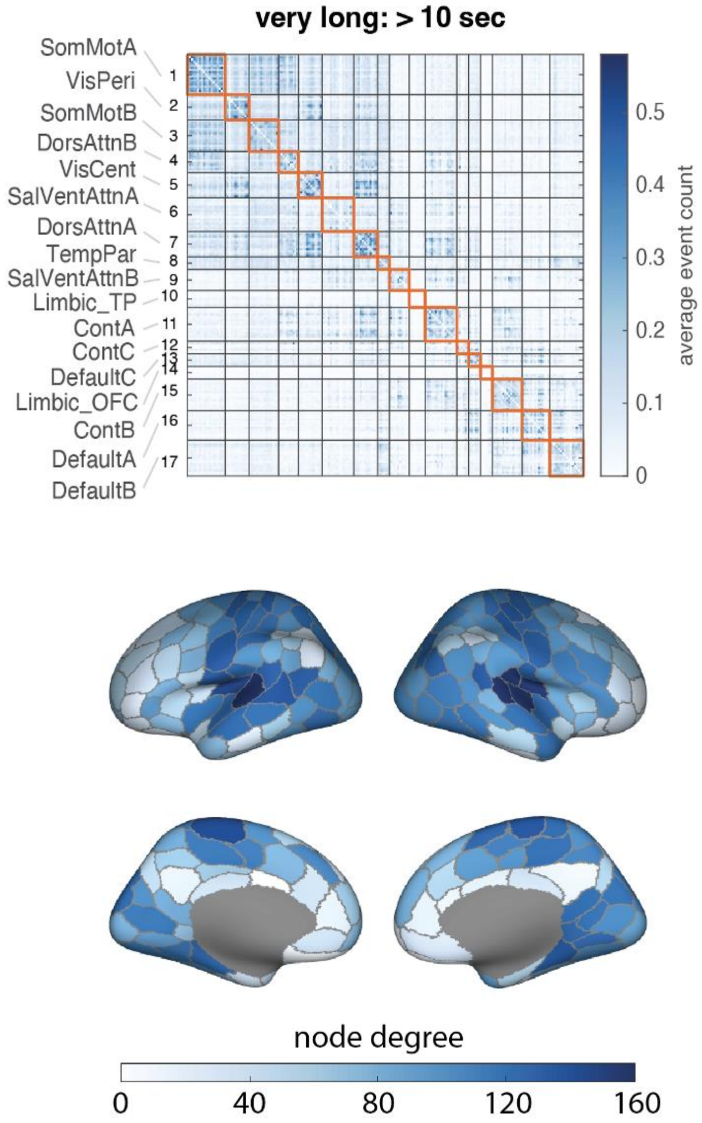




G. Cooper et al. "Where the present gets remembered: Sensory regions communicate with the brain over the longest timescales." bioRxiv 2023

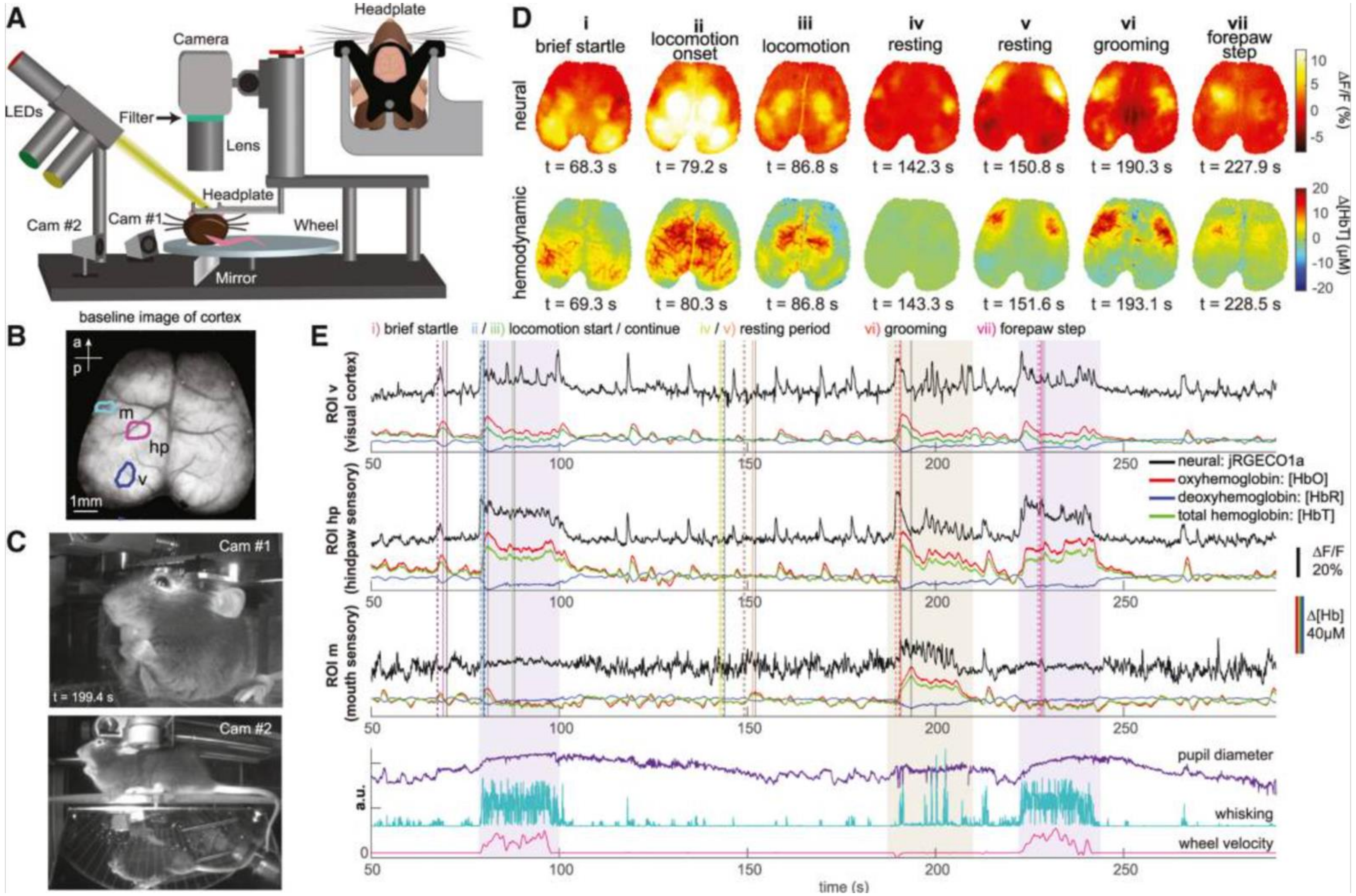
"…emphasizing the role of sensory regions as sites of integration across timescales."

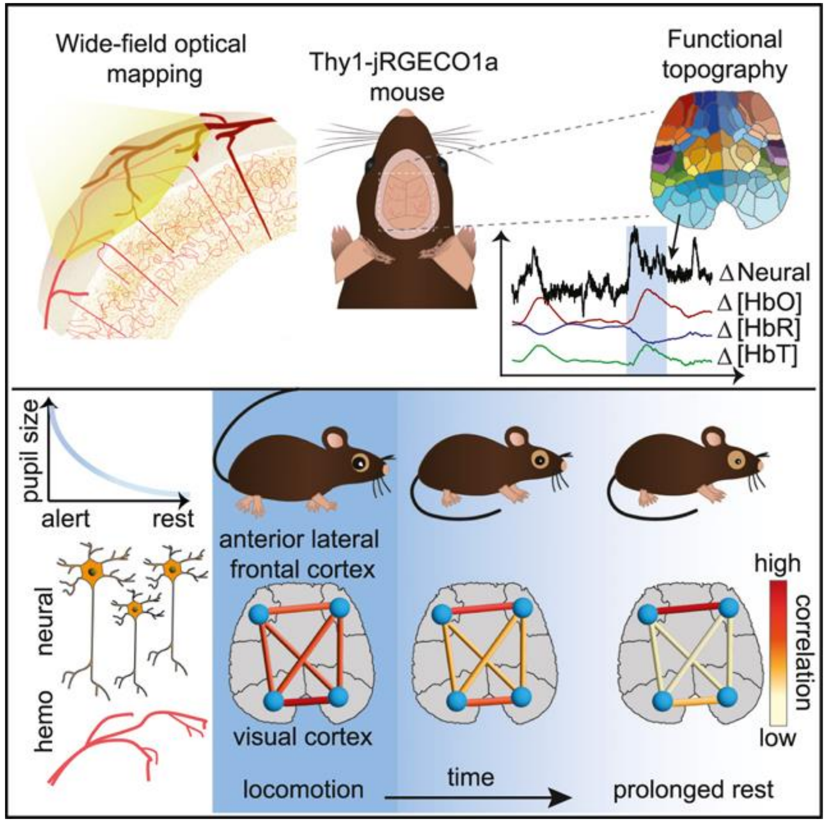




Is event duration a proxy for communication time scale?

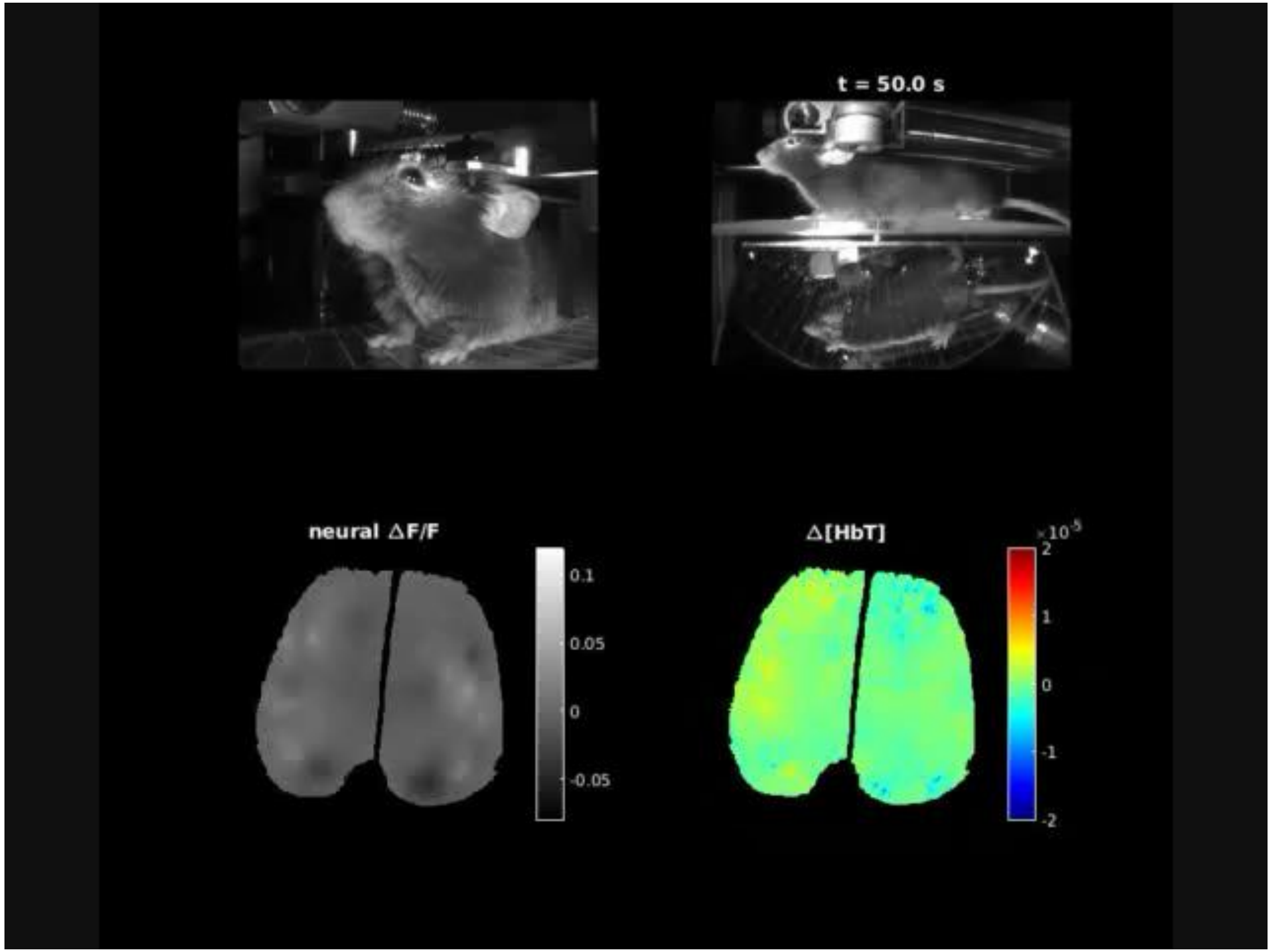
Simultaneous Wide Field Calcium and Hemodynamic Imaging During Rest and Engagement



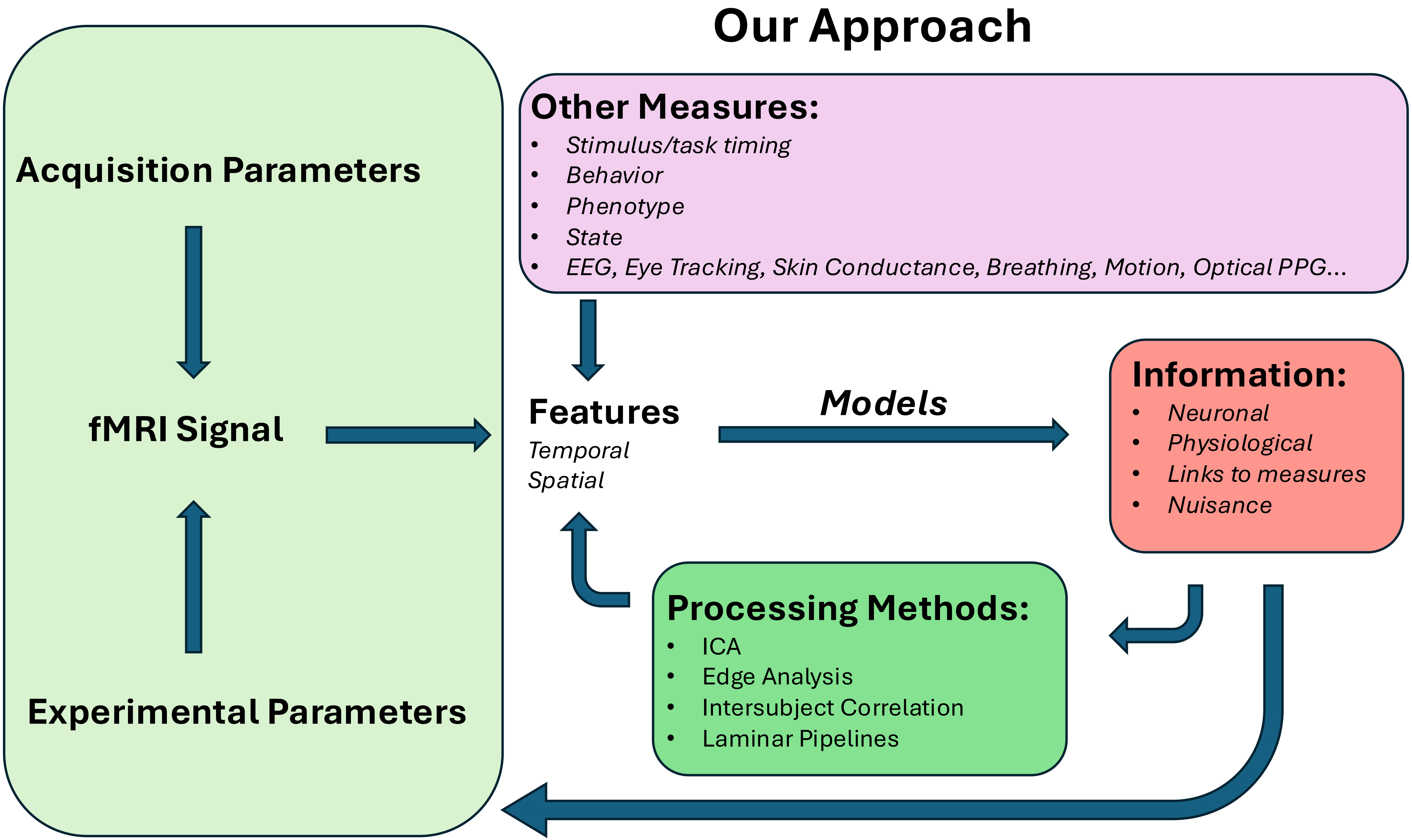


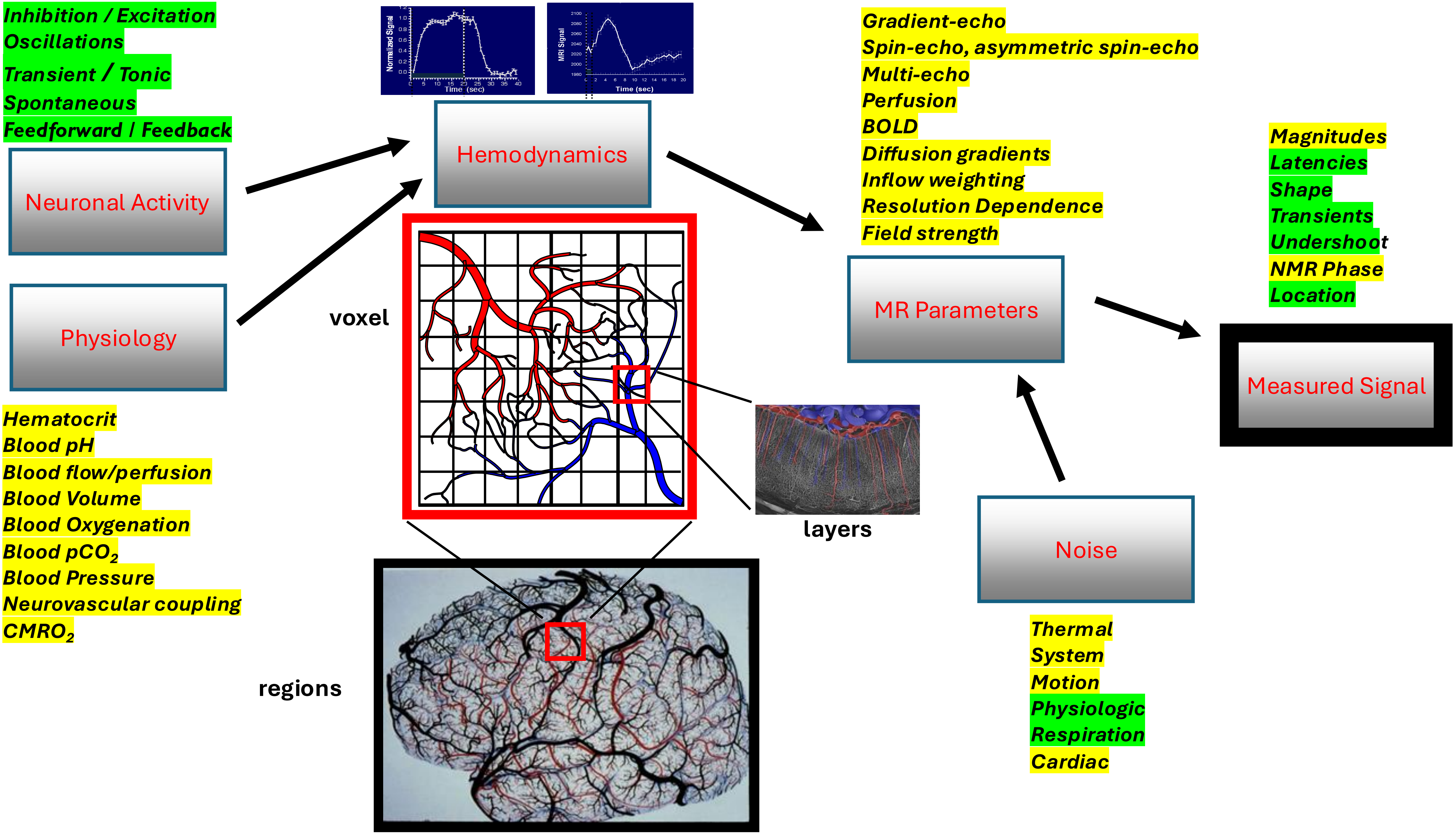
Shahsavarani et al., 2023, Cell Reports 42, 112527

neural, jRGECO1a: % fluorescence change after hemodynamic correction ΔF/F
hemodynamic, Δ[HbT]: Δ[HbO] + Δ[HbR]



Shahsavarani et al., 2023, Cell Reports 42, 112527


Our Approach
Acquisition Parameters
fMRI Signal
Experimental Parameters
Other Measures:
Stimulus/task timing
Behavior
Phenotype
State
EEG, Eye Tracking, Skin Conductance, Breathing, Motion, Optical PPG…
Features
Temporal
Spatial
Models
Information:
Neuronal
Physiological
Links to measures
Nuisance
Processing Methods:
ICA
Edge Analysis
Intersubject Correlation
Laminar Pipelines


Inhibition / Excitation
Oscillations
Transient / Tonic
Spontaneous
Feedforward / Feedback
Neuronal Activity
Physiology
Hematocrit
Blood pH
Blood flow/perfusion
Blood Volume
Blood Oxygenation
Blood pCO_2
Blood Pressure
Neurovascular coupling
$CMRO_2$
Normalized Signal
Time (sec)
MRI Signal
Time (sec)
Hemodynamics
voxel
layers
regions
Gradient-echo
Spin-echo, asymmetric spin-echo
Multi-echo
Perfusion
BOLD
Diffusion gradients
Inflow weighting
Resolution Dependence
Field strength
MR Parameters
Noise
Thermal
System
Motion
Physiologic
Respiration
Cardiac
Magnitudes
Latencies
Shape
Transients
Undershoot
NMR Phase
Location
Measured Signal

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Yoichi Miwawaki

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Linqing Li

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Hoan Le

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Marcela Montequin

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