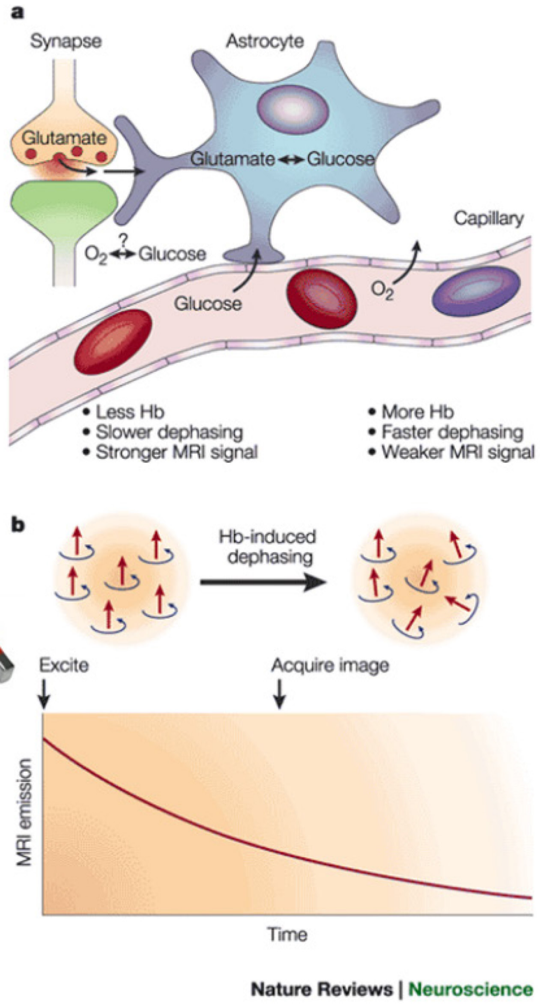
The importance of hemodynamics and blood arrival time in acquiring, analyzing, and modelling fMRI data

N. Colenbier, A. Johri, K. Clauw, G. Wu, G. Ferrazzi, D. Marinazzo

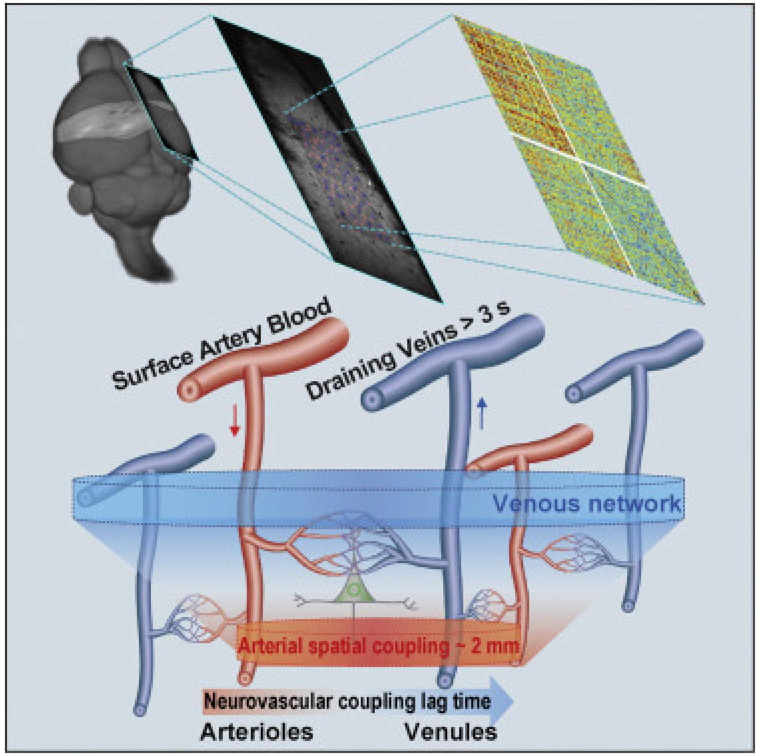
Department of Data Analysis, Ghent University

EBRAINS 2.0 has received funding from the European Union's Research and Innovation Program Horizon Europe under Grant Agreement No. 101147319.

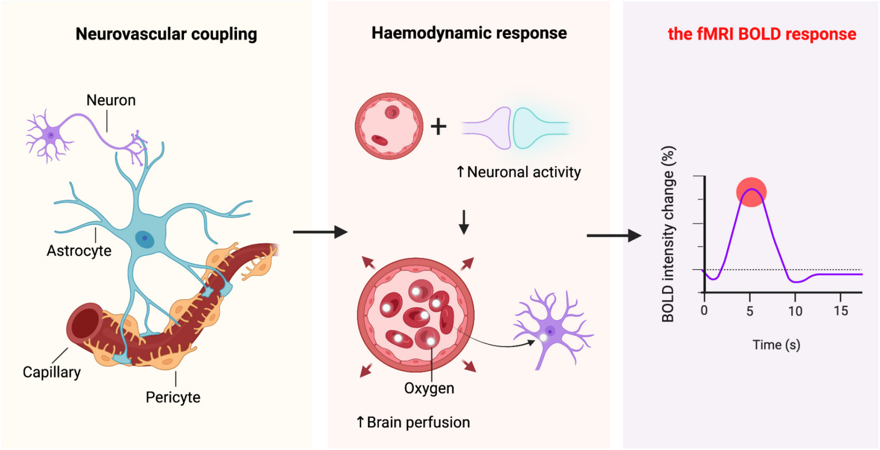
Through the hemodynamic lens



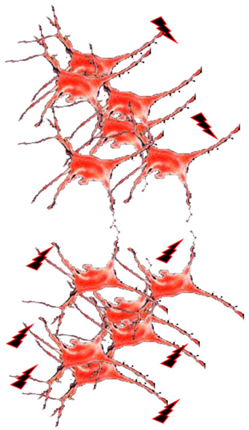
David J. Heeger & David Ress
Nature Reviews Neuroscience **3**, 142-151

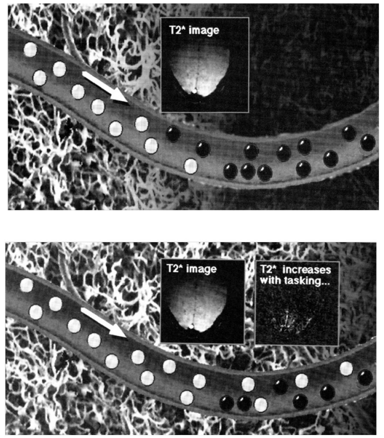


He et al. Neuron 97, 2018

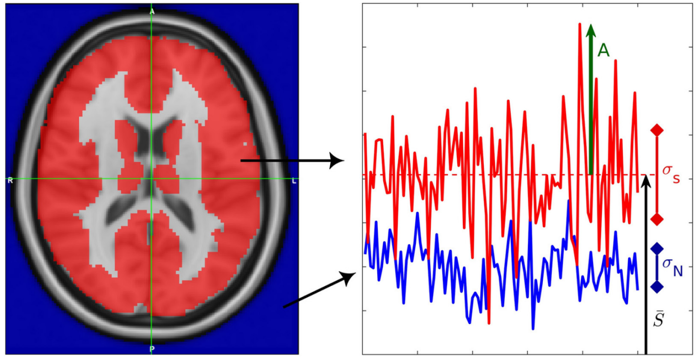


fMRI needs a contrast, and a model for activation …





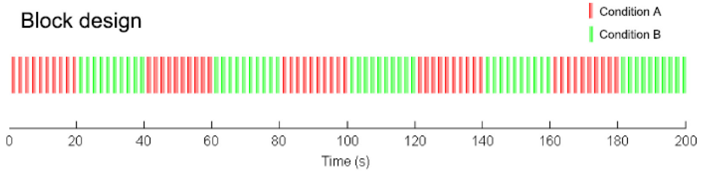
From Mosley & Glover (1995)

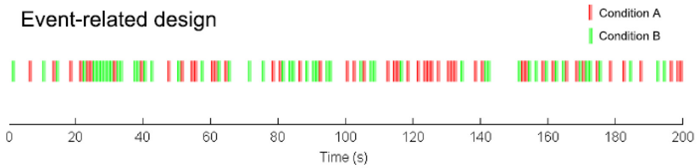


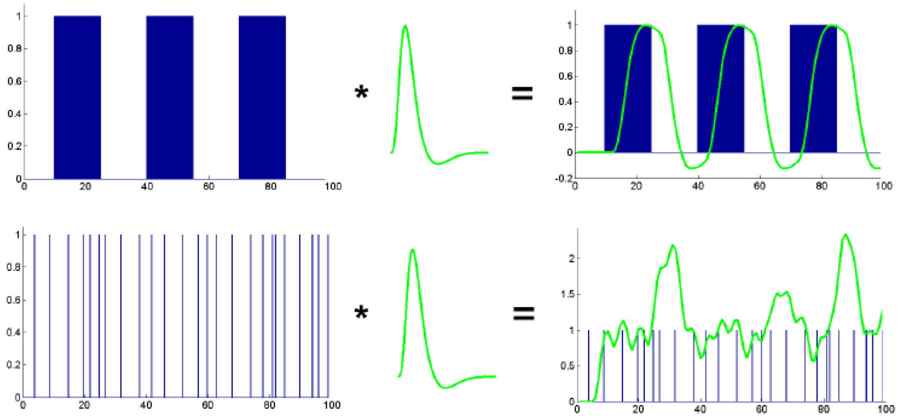
Signal to noise: $\frac{\bar{S}}{\sigma_N}$

Contrast to noise: $\frac{A}{\sigma_N}$

Temporal signal to noise: $\frac{\bar{S}}{\sigma_S}$







$$Y = X \,.\, \boxed{\beta} + \varepsilon$$

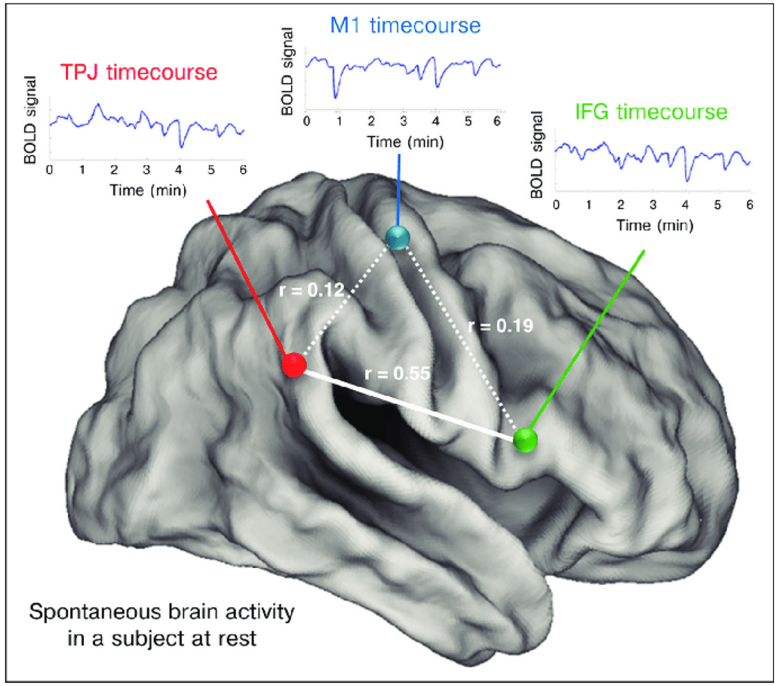
observed data at a single voxel

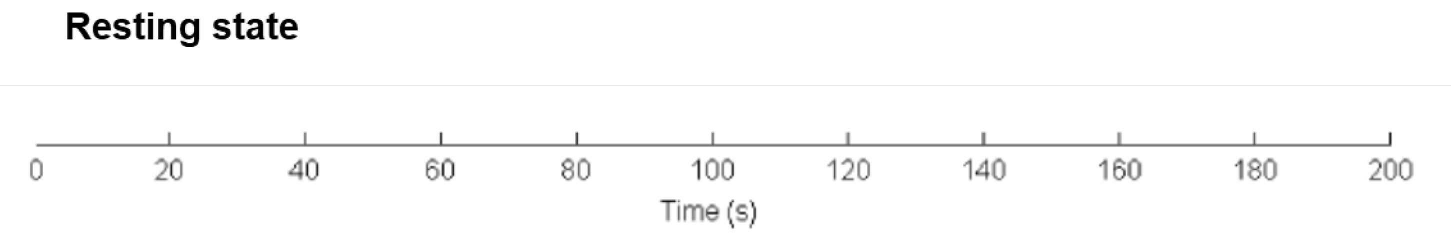
design matrix

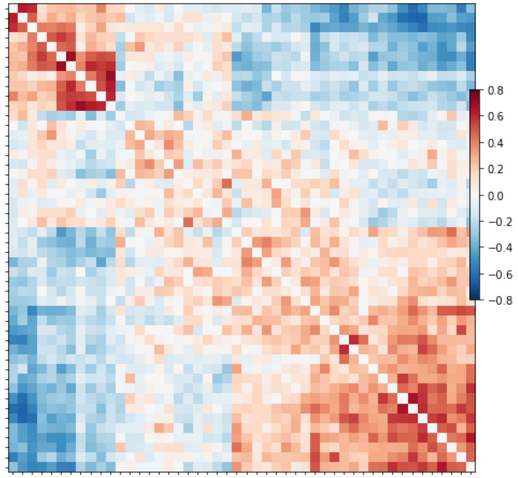
estimated parameters

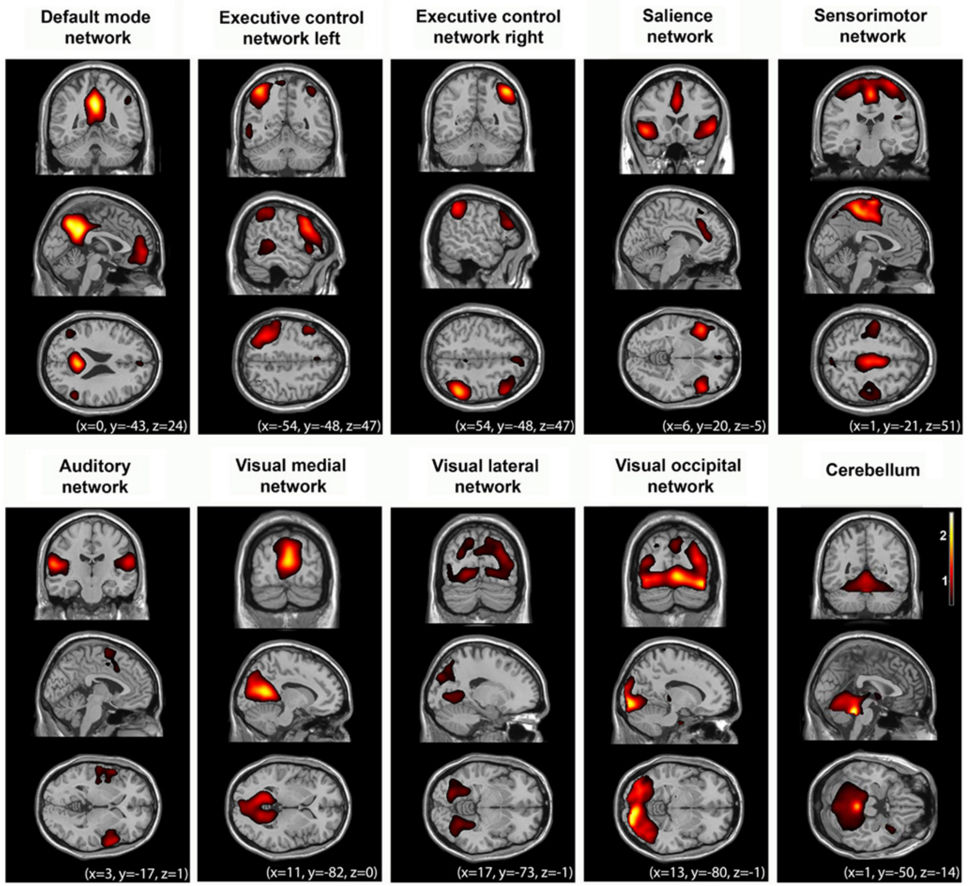
error

… but BOLD signal also fluctuates on its own



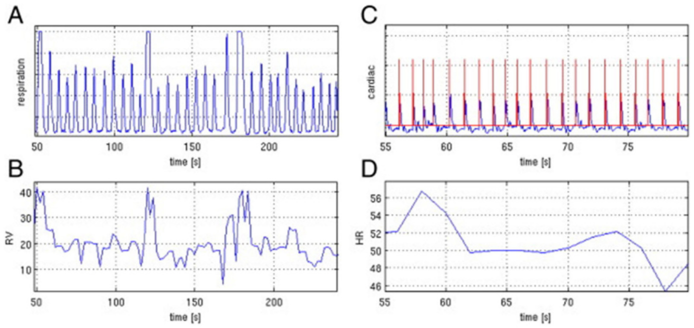






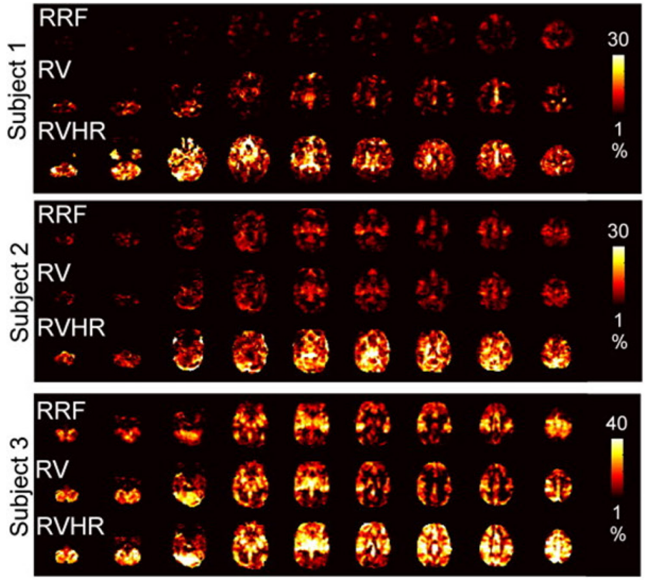
Co-funded by the European Union

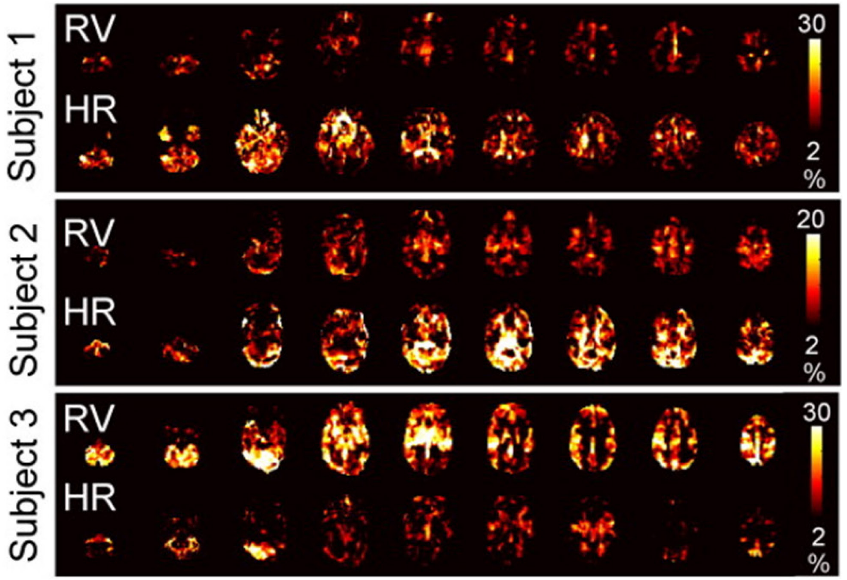
Cardiac and respiratory response function



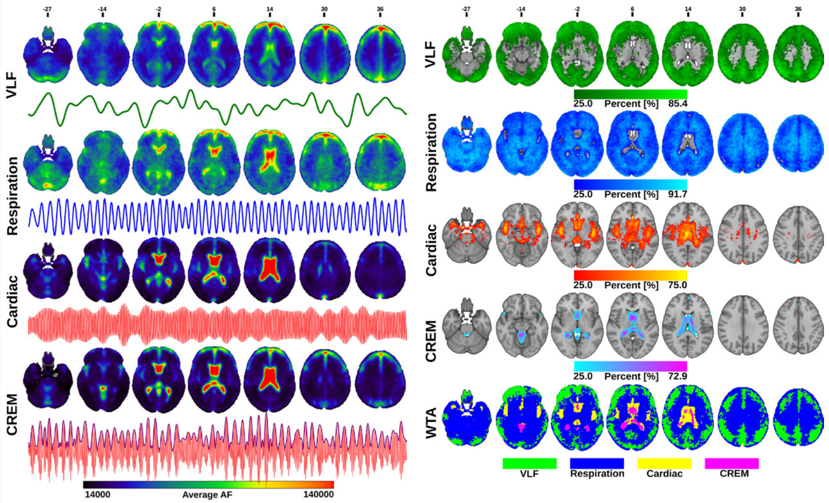
Example of physiological time courses for 1 subject, showing (A) respiration belt measurements, (B) the calculated RV, (C) cardiac cycle with triggers, and (D) the calculated HR. Note that (A, B) are displayed on a different time scale than (C, D).

Chang et al. NeuroImage 2009

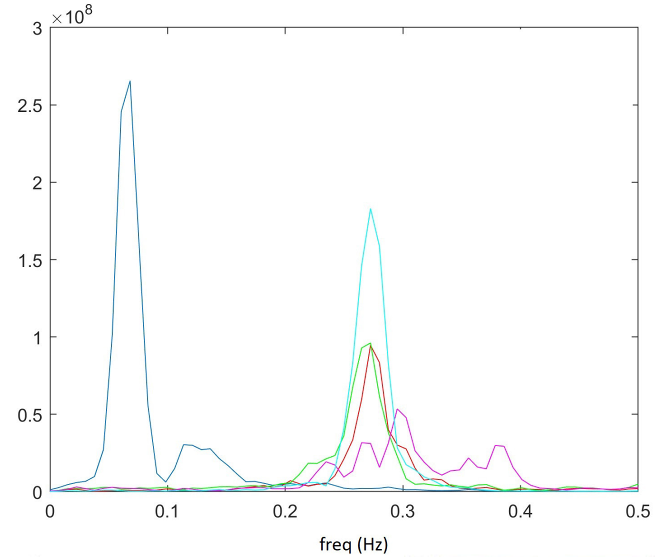


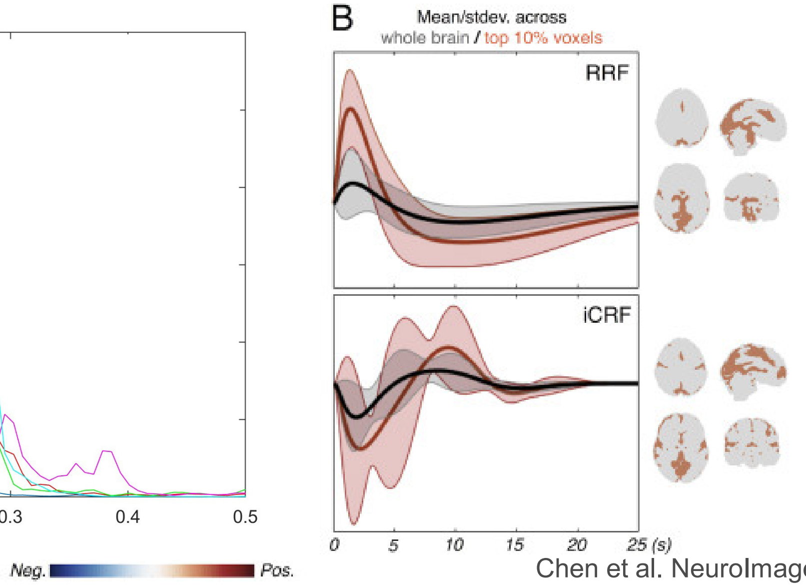


Chang et al. NeuroImage 2009



Raitamaa et al. HBM 2021





Chen et al. NeuroImage 2020

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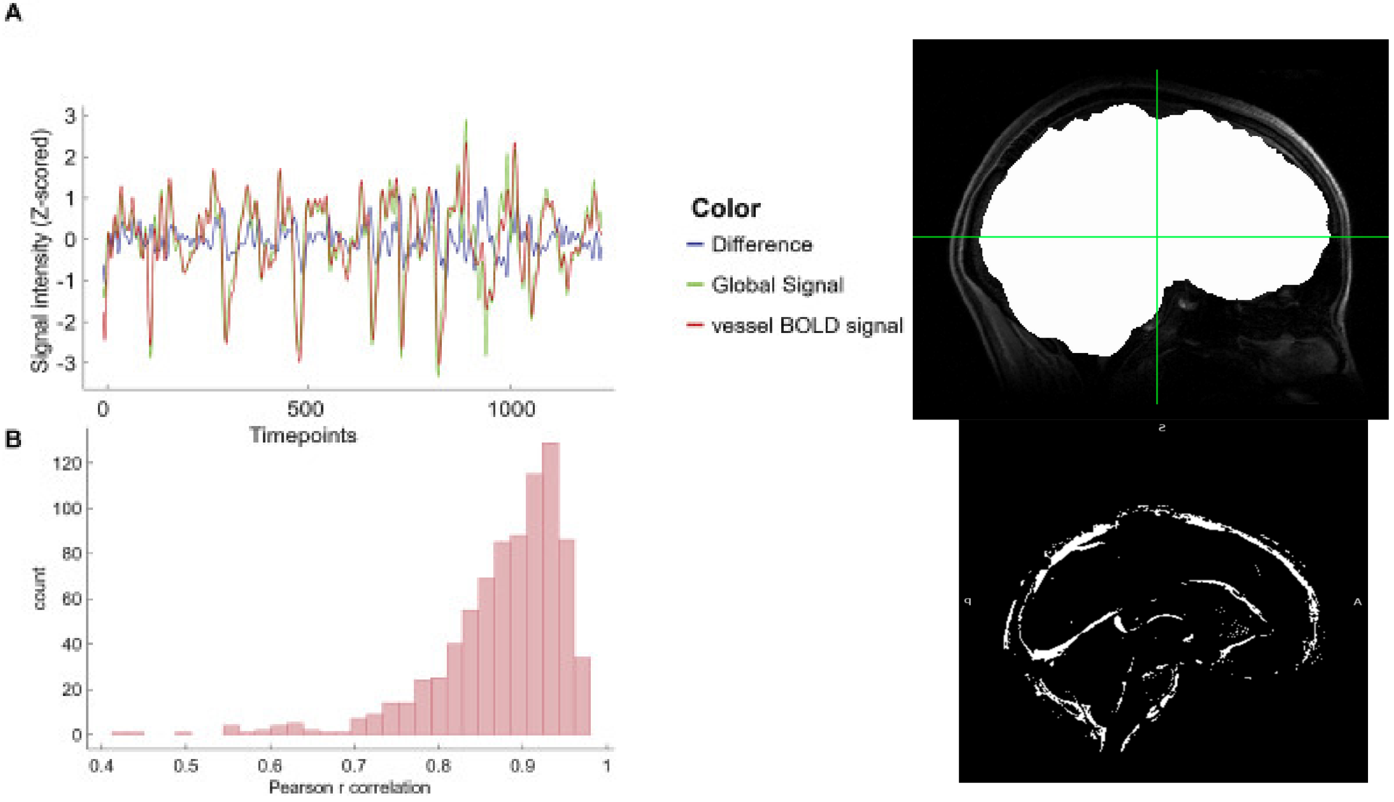
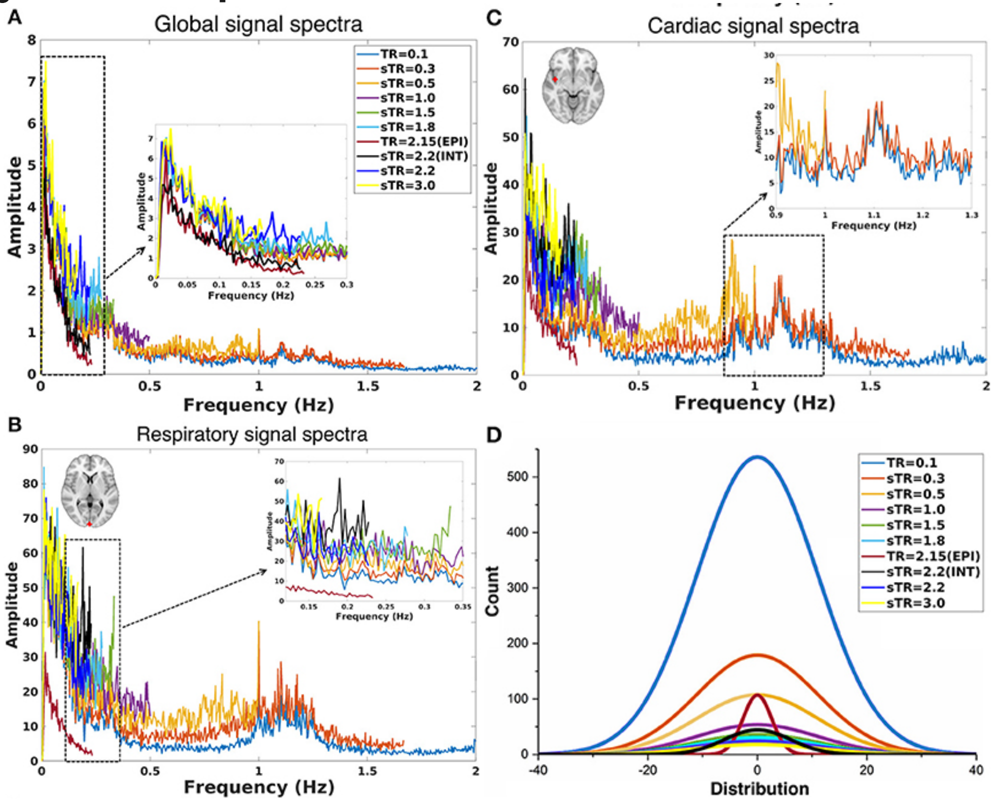
Hemodynamics, heartbeat and respiration are not “just noise”

- Some processing methods claim to “remove” physiological confounders, but this is not possible since physiology literally makes the BOLD signal
- Physiological fluctuations (and/or their aliases) have often the same scale/frequency of neural activity, and similar dynamic patterns



Colenbier et al. Neuroimage 2020



Huotari et al. Front. Neurosci. 2019

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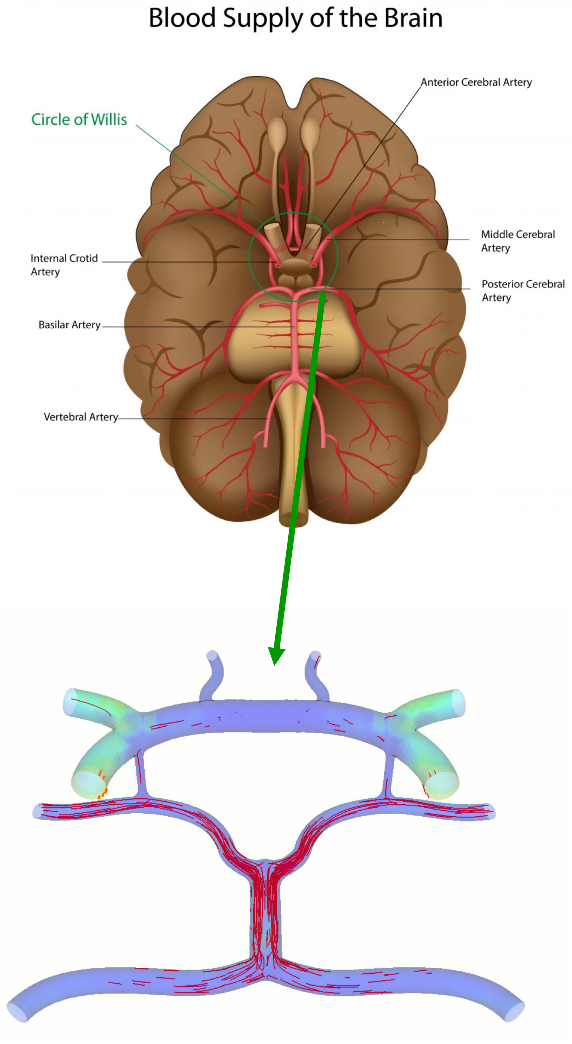
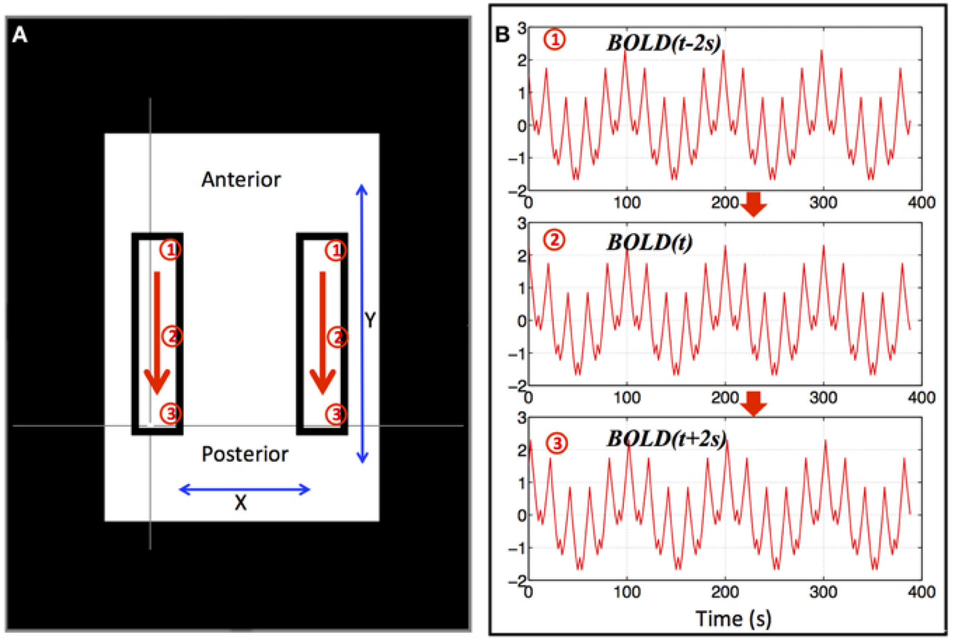
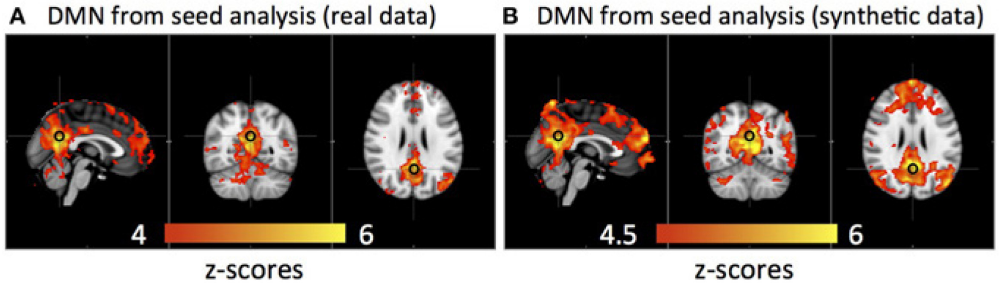
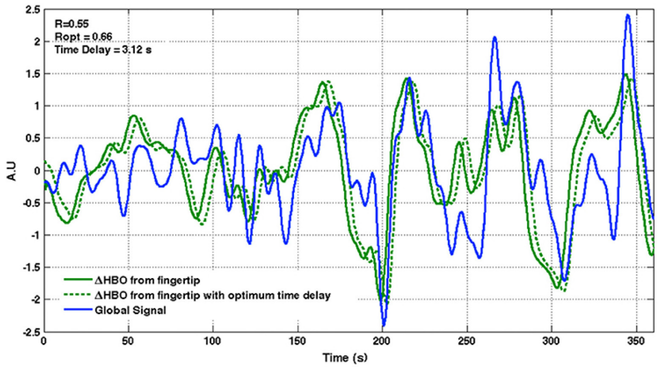
Blood flow

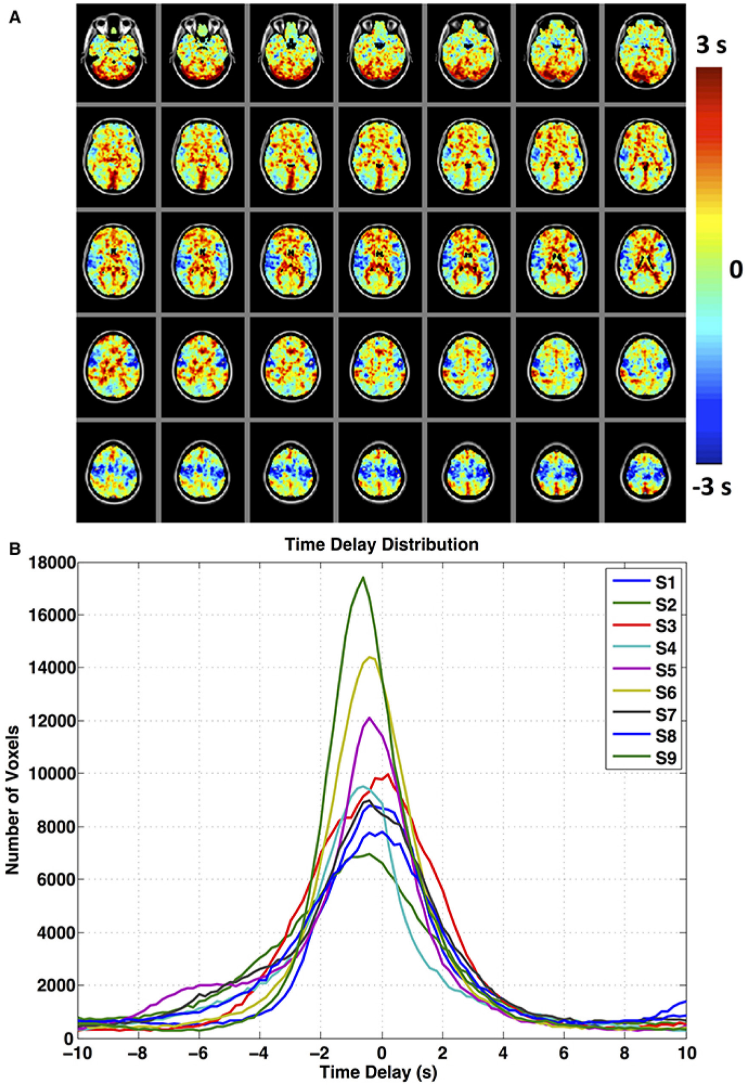


Ansys, 2024









Tong and Frederick Human Brain Mapping 2014
Tong et al. Front. Hum. Neurosci. 2015
Erdogan et al. Front. Hum. Neurosci. 2016
Chen et al. Neuroimage 2020

Co-funded by the European Union

EBRAINS 2.0

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Blood flow inflates FC estimates

Brain-wide functional connectivity artifactually inflates throughout functional magnetic resonance imaging scans

Cole Korponay, Amy C. Janes & Blaise B. Frederick

Nature Human Behaviour **8**, 1568–1580 (2024) | Cite this article

Abstract

Functional magnetic resonance imaging (fMRI) is a central tool for investigating human brain function, organization and disease. Here, we show that fMRI-based estimates of functional brain connectivity artifactually inflate at spatially heterogeneous rates during resting-state and task-based scans. This produces false positive connection strength changes and spatial distortion of brain connectivity maps. We demonstrate that this artefact is driven by temporal inflation of the non-neuronal, systemic low-frequency oscillation (sLFO) blood flow signal during fMRI scanning and is not addressed by standard denoising procedures. We provide evidence that sLFO inflation reflects perturbations in cerebral blood flow by respiration and heart rate changes that accompany diminishing arousal during scanning, although the mechanisms of this pathway are uncertain. Finally, we show that adding a specialized sLFO denoising procedure to fMRI processing pipelines mitigates the artifactual inflation of functional connectivity, enhancing the validity and within-scan reliability of fMRI findings.

Rapidtide

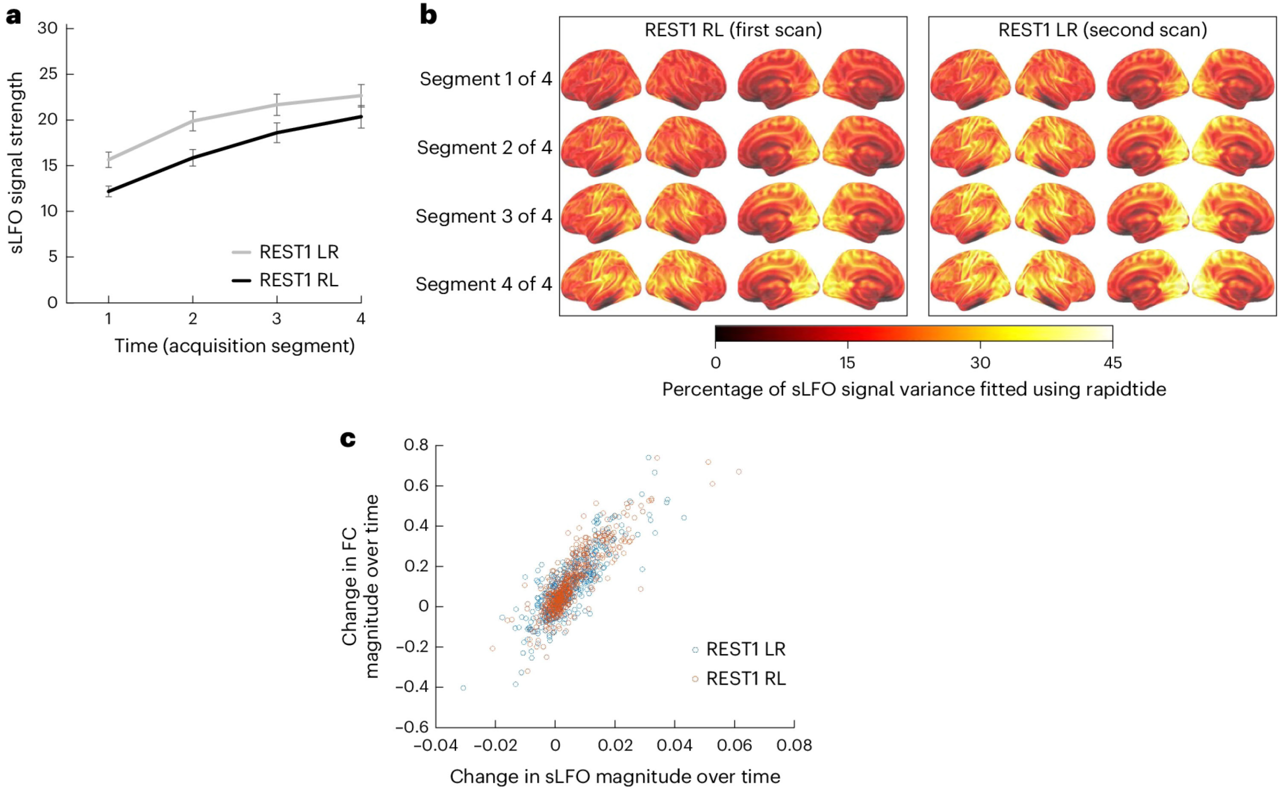
Rapidtide is a suite of python programs used to perform rapid time delay analysis on functional imaging data to find time lagged correlations between the voxelwise time series and other time series, both in the LFO band (rapditide2) and now in the cardiac band (happy).

pypi v2.9.9.5 | python 3.9 | 3.10 | 3.11 | 3.12 | License Apache 2.0 | docs unknown | circleci passing

codecov 35% | DOI 10.5281/zenodo.814990 | NIH R01-NS097512-01A1

Citing rapidtide

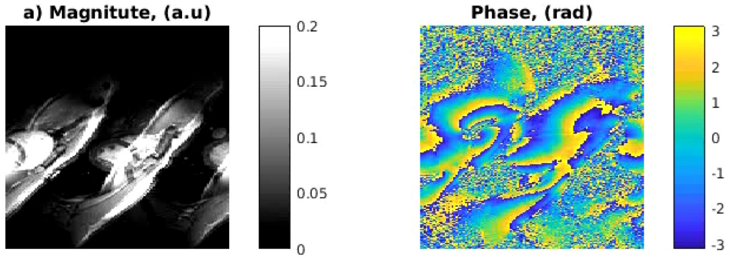
Frederick, B, rapidtide [Computer Software] (2016-2024). Available from https://github.com/bbfrederick/rapidtide. doi:10.5281/zenodo.814990

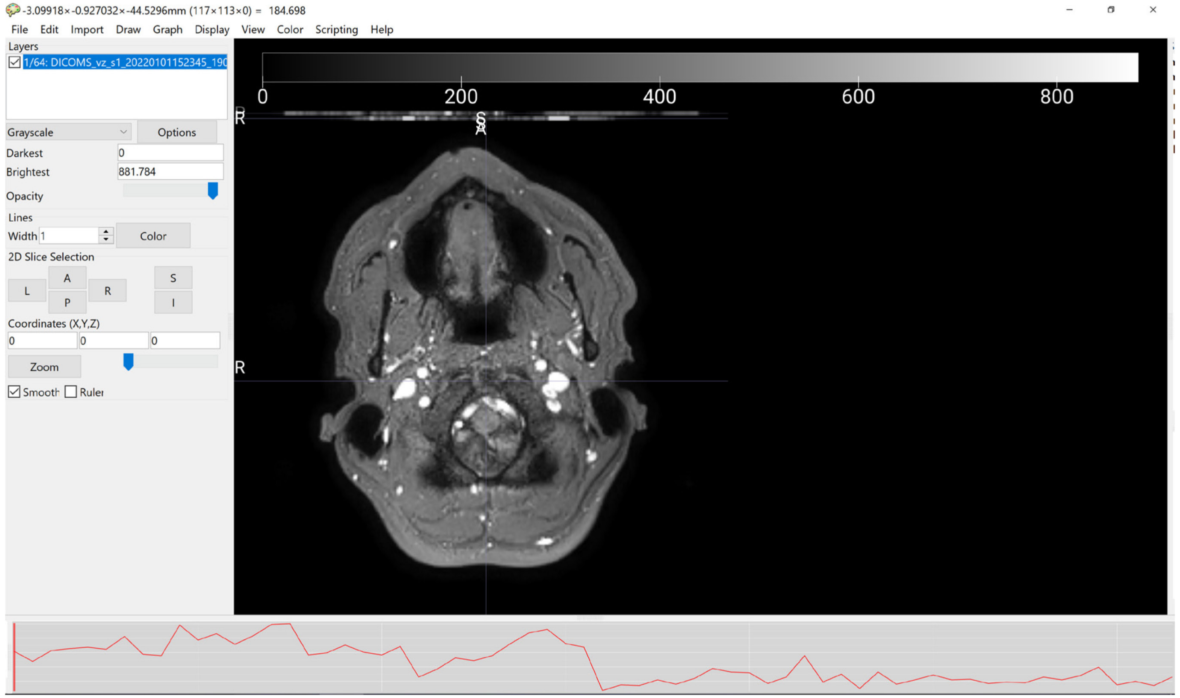


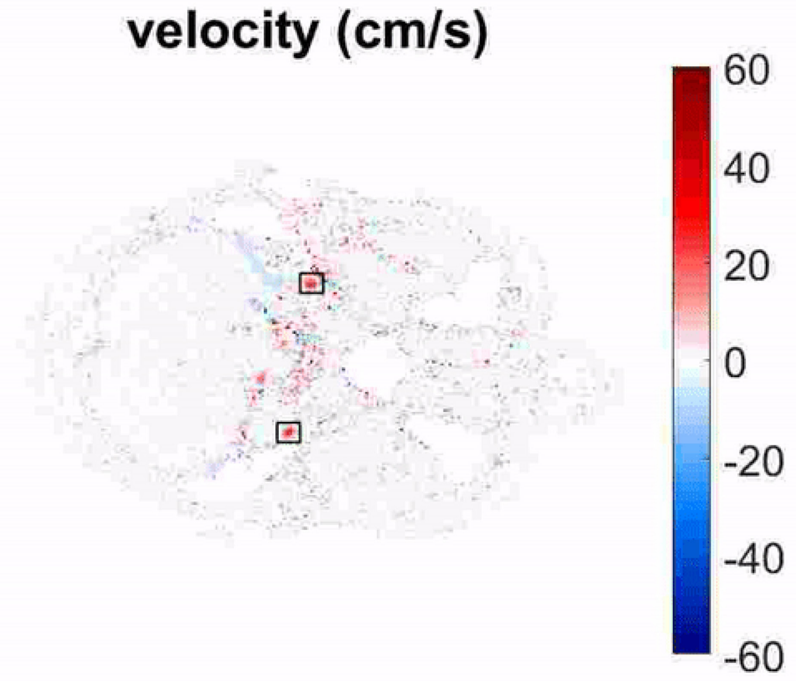
Blood flow velocity in brain plumbing

Autocalibrated multiband CAIPIRINHA with through-time encoding: Proof of principle and application to cardiac tissue phase mapping

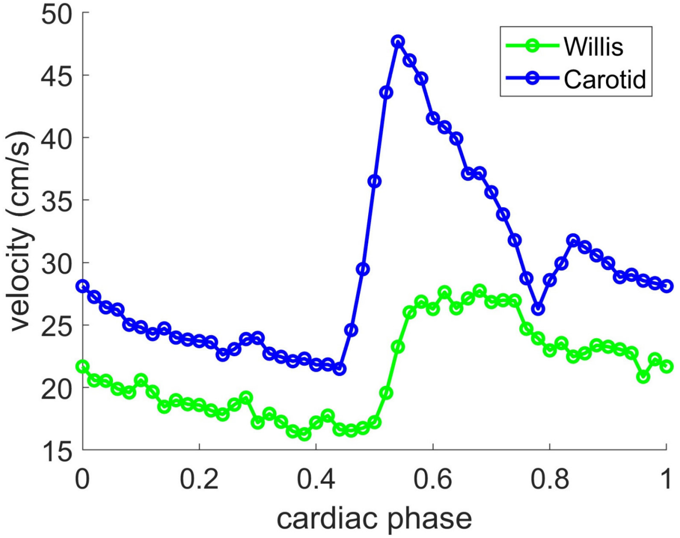
Giulio Ferrazzi, Jean Pierre Bassenge, Clarissa Wink, Alexander Ruh, Michael Markl, Steen Moeller, Gregory J. Metzger, Bernd Ittermann, Sebastian Schmitter

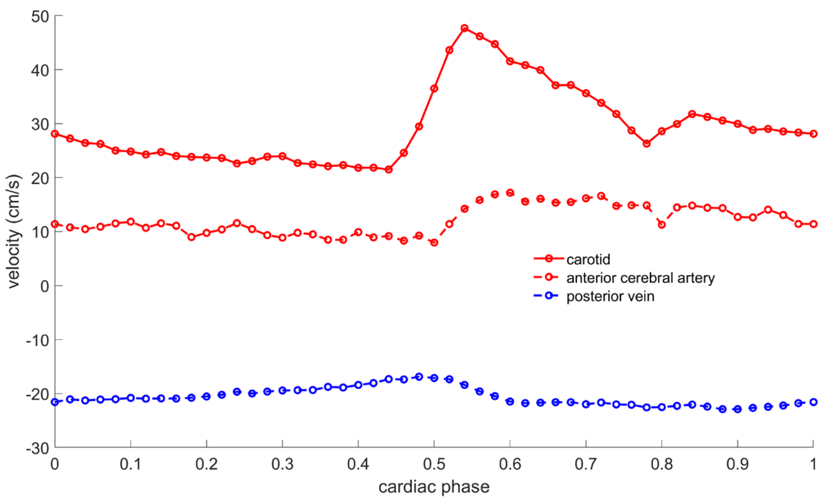


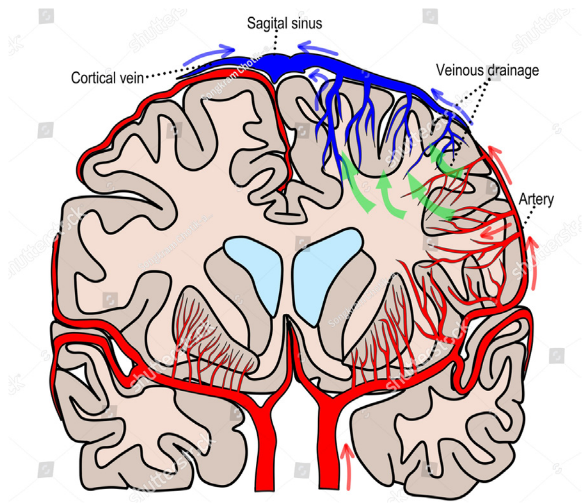


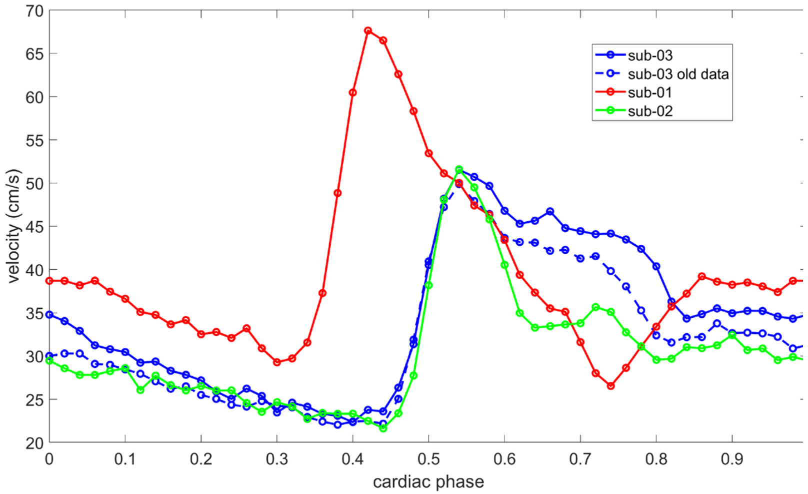


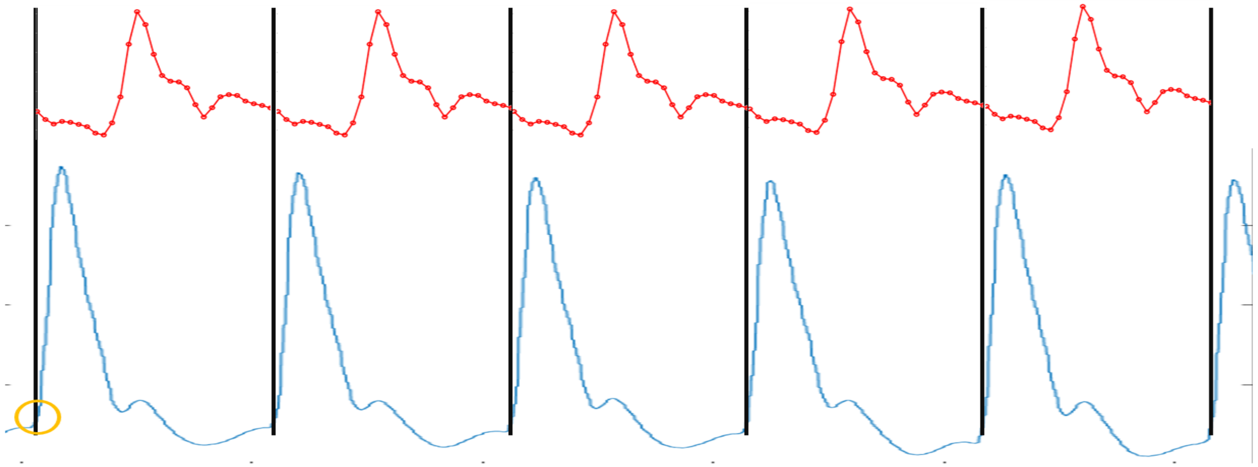
Blood flow velocity in brain plumbing











Co-funded by the European Union

A functional role for phase contrast data

September 12 2025

Visual stimulus-evoked blood velocity responses in individual human posterior cerebral arteries measured with dynamic phase-contrast functional MR angiography

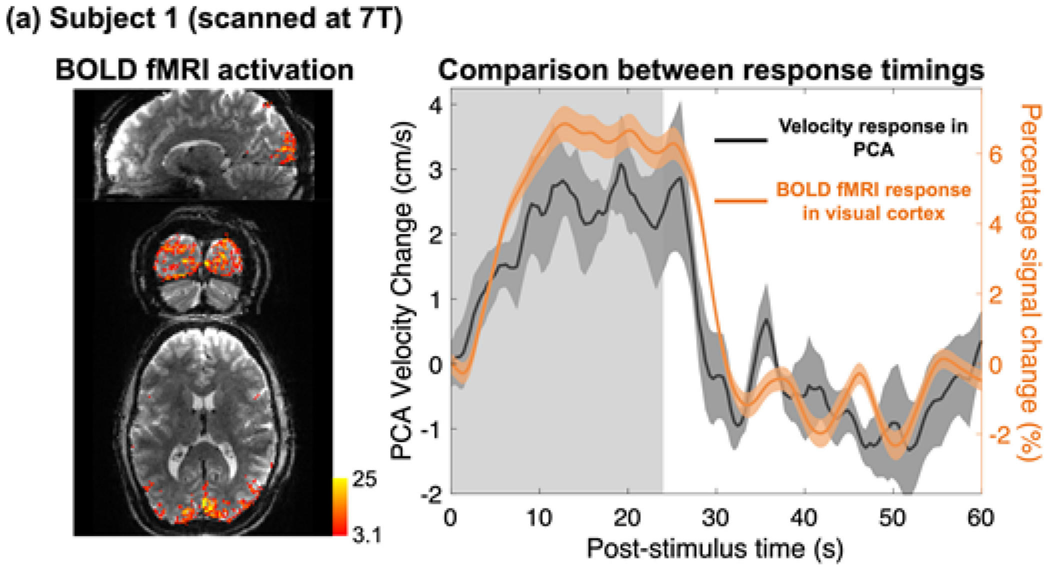
Zhangxuan Hu, Sébastien Proulx, Grant A. Hartung, Daniel E. P. Gomez, Jingyuan E. Chen, Divya Varadarajan, Elif Gökçal, Saskia Bollmann, Can Ozan Tan, M. Edip Gurol, Jonathan R. Polimeni

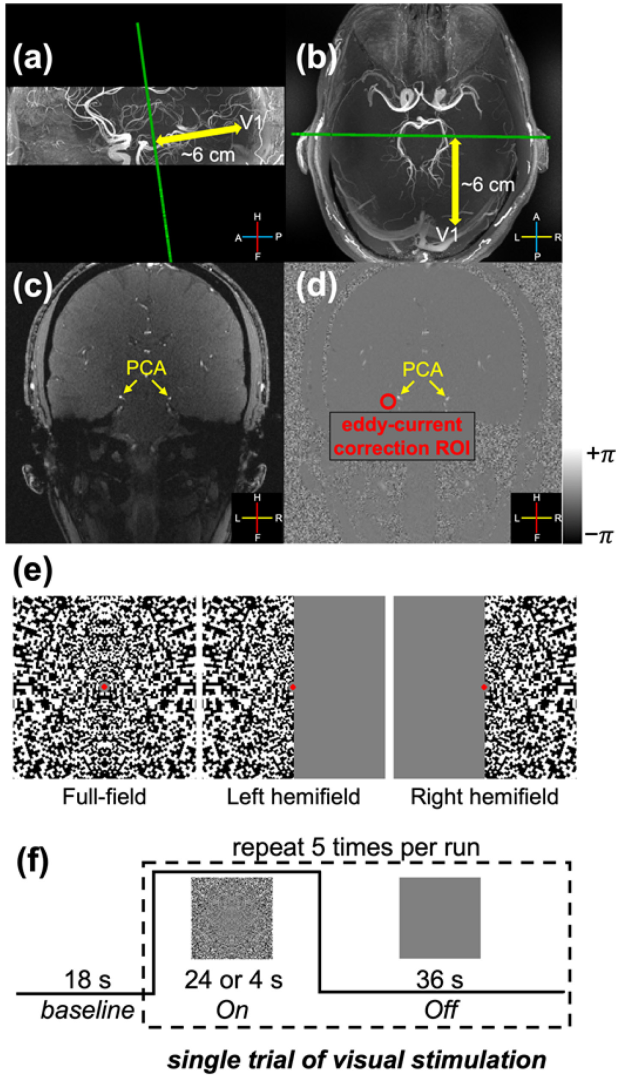
Check for updates

Author and Article Information

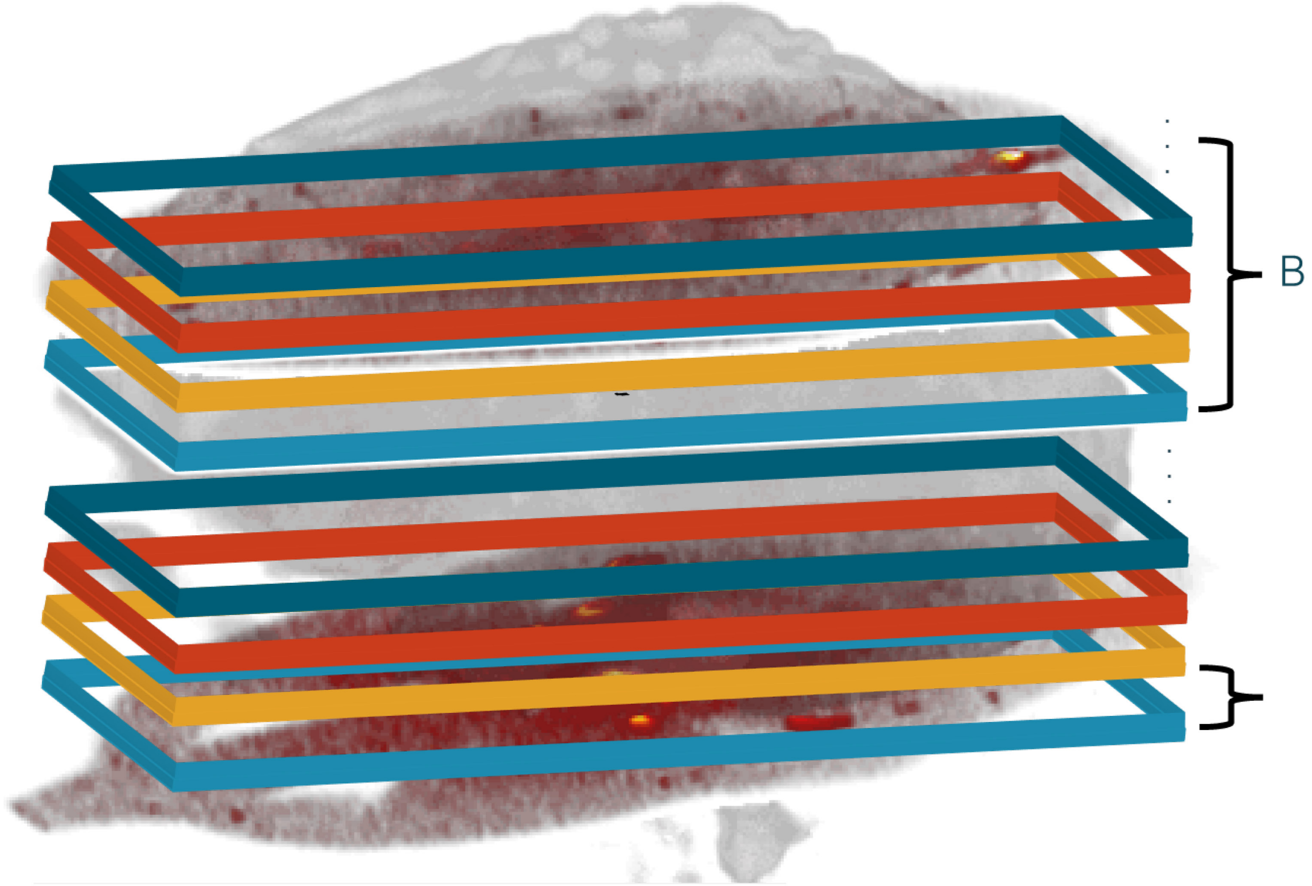
Imaging Neuroscience (2025) 3: IMAG.a.148.

https://doi.org/10.1162/IMAG.a.148 **Article history**





Cardiac pulsatility from (multiband) BOLD data



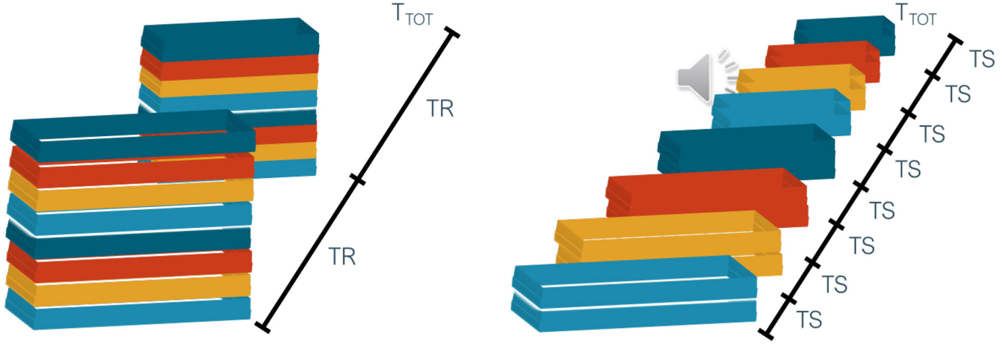
Z [Total slices]

MB [Multiband factor]

$$B = \frac{Z}{MB}$$

B [Number of RF excitations per imaging volume]

TS [Time between excitations]

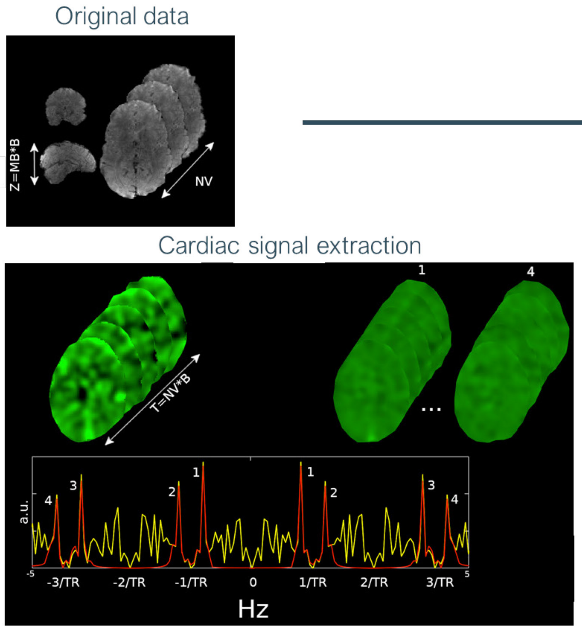


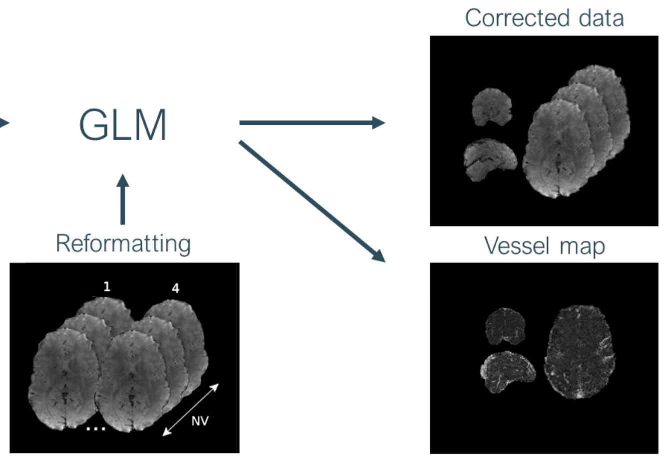
Extraction of the cardiac waveform from simultaneous multislice fMRI data using slice sorted averaging and a deep learning reconstruction filter

Serdar Aslan [a b], Lia Hocke [a b], Nicolette Schwarz [a b], Blaise Frederick [a b]

data reformatted along slice and temporal domains, then Fourier transformed

Creating a cardiac regressor



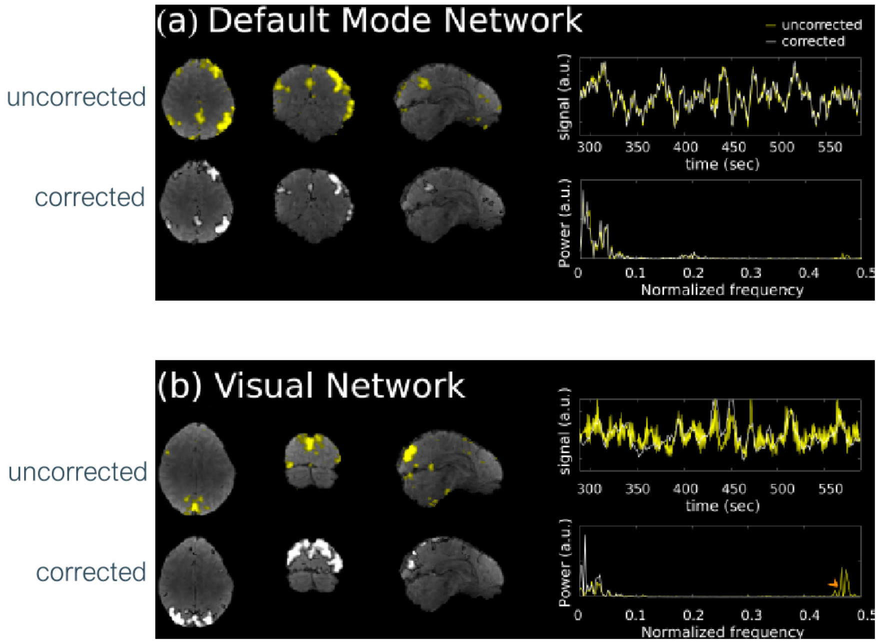


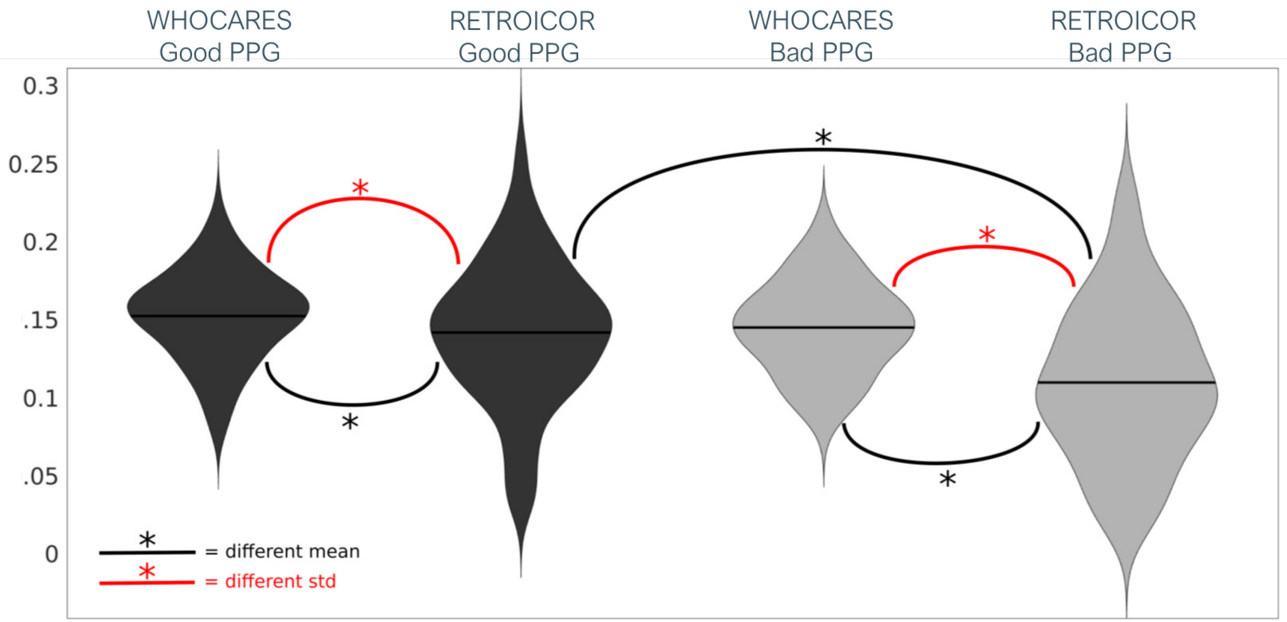
Upsample from TR to TS = TR/MB

Temporal Fourier transform to extract 8 cardiac signal peaks from the hyper-resolved time-series

Bandpass filters (±0.2 Hz) isolate each cardiac component; a GLM constructs a voxel-wise cardiac regressor

Computing mutual information (MI)





PAPER • OPEN ACCESS

WHOCARES: WHOle-brain CArdiac signal REgression from highly accelerated simultaneous multi-Slice fMRI acquisitions

Nigel Colenbier[6,1], Marco Marino[6,1,2], Giorgio Arcara[1], Blaise Frederick[3,4], Giovanni Pellegrino[1], Daniele Marinazzo[1,5] and Giulio Ferrazzi[7,1]

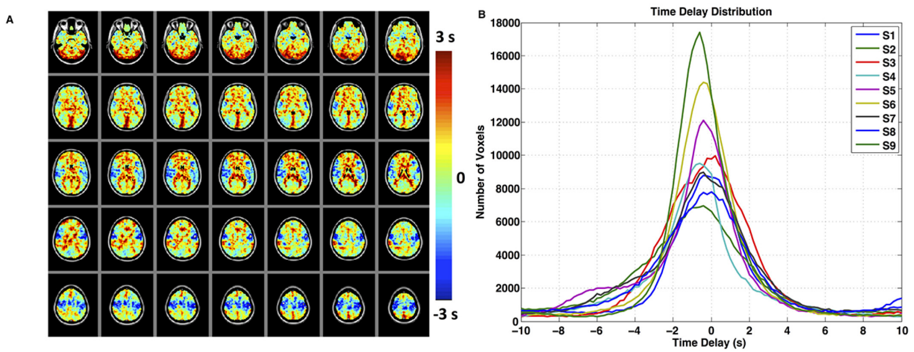
Published 6 September 2022 • © 2022 The Author(s). Published by IOP Publishing Ltd

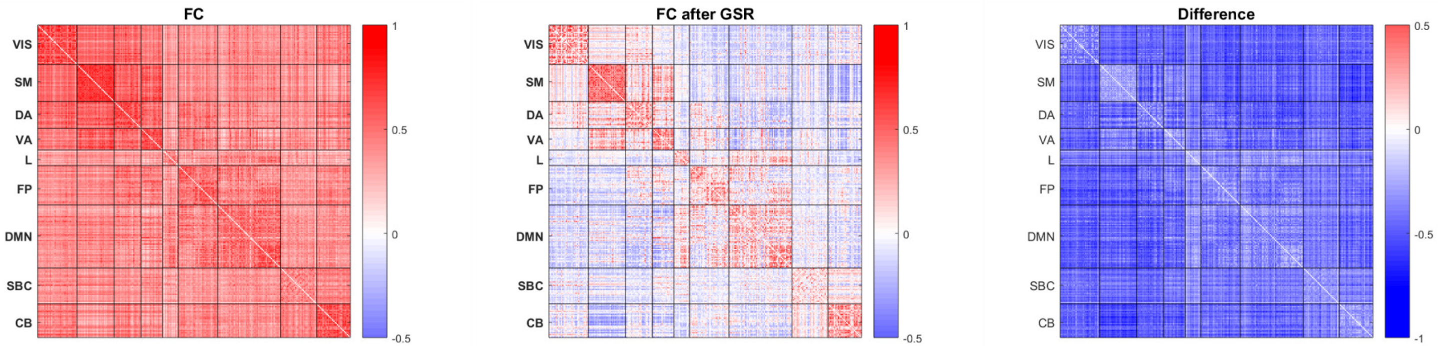
Journal of Neural Engineering, Volume 19, Number 5

Citation Nigel Colenbier *et al* 2022 *J. Neural Eng.* **19** 056006

DOI 10.1088/1741-2552/ac8bff

Blood flow and global signal regression





Brain Connectivity
Volume 2, Issue 1, 1 February 2012, Pages 25-32

Trouble at Rest: How Correlation Patterns and Group Differences Become Distorted After Global Signal Regression (Article)

Saad, Z.S.[a], Gotts, S.J.[b], Murphy, K.[c], Chen, G.[a], Jo, H.J.[a], Martin, A.[b], Cox, R.W.[a]

Letter

On Global fMRI Signals and Simulations

Jonathan D. Power [1], Timothy O. Laumann [2], Mark Plitt [3], Alex Martin [4], Steven E. Petersen [5]

Spotlight

Mixed Signals: On Separating Brain Signal from Noise

Lucina Q. Uddin [1, 2]

Towards a consensus regarding glc
resting state functional connectivity

Kevin Murphy [a, b], Michael D. Fox [c, d, e]

Neuroimage. 2009 Feb 1;44(3):893-905. doi: 10.1016/j.neuroimage.200

The impact of global signal regression o introduced?

Murphy K[1], Birn RM, Handwerker DA, Jones TB, Bandettini PA.

NeuroImage
Volume 146, 1 February 2017, Pages 609-625

Sources and implications of whole

Power, J.D.[a], Plitt, M.[a], Laumann, T.O.[b]

Benchmarking of participant-level con
strategies for the control of motion art
functional connectivity

Rastko Ciric [a], Daniel H. Wolf [a], Jonathan D. Power [b], David R. Roa
Russell T. Shinohara [c], Mark A. Elliott [d], Simon B. Eickhoff [e, f], Chri
Gur [a, d], Danielle S. Bassett [g, h], Theodore D. Satterthwaite [a]

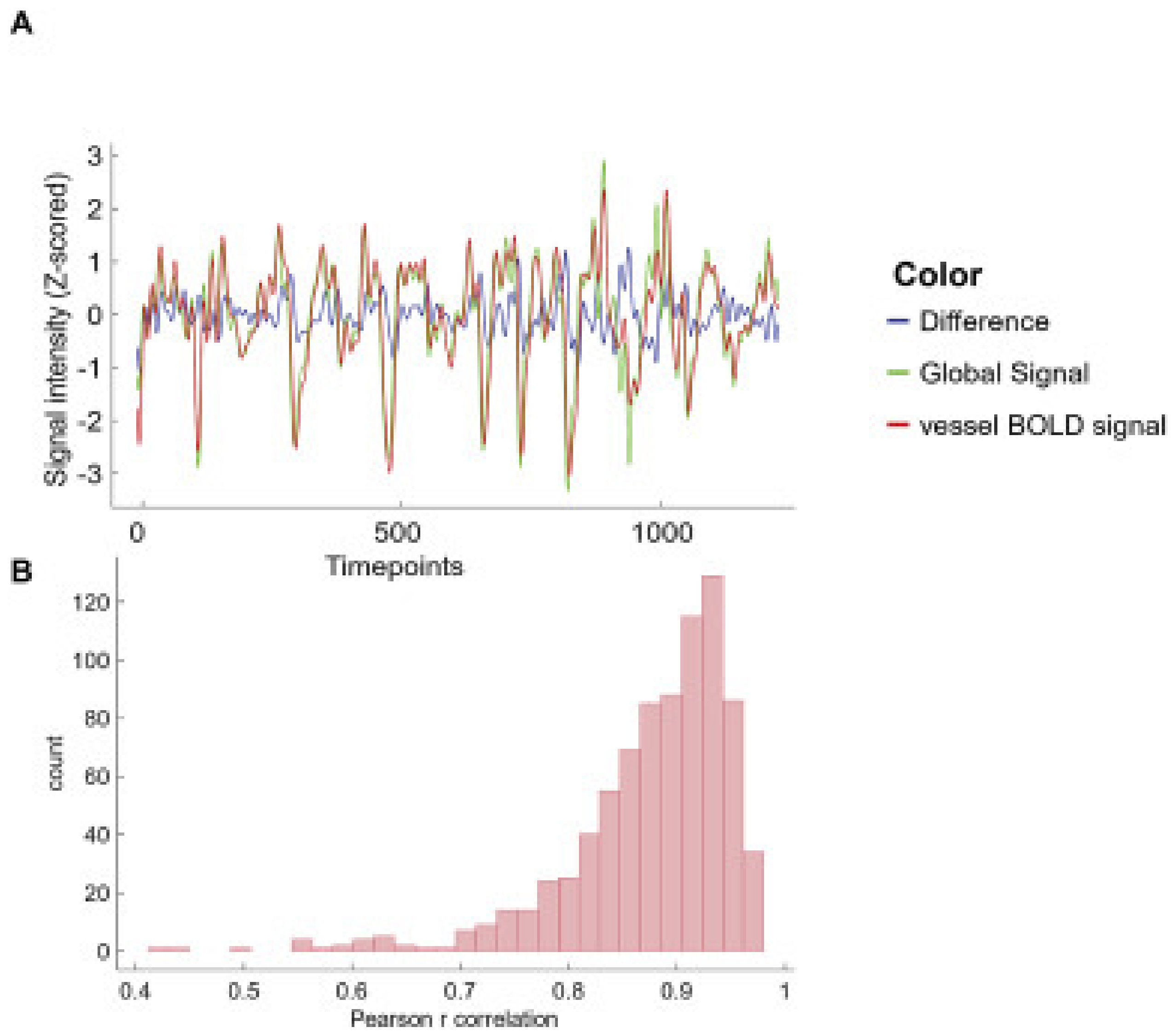
To regress out or not? An update on the fMRI global signal debate

Athena Demertzi Organizer
GIGA Institute, University of Liège
Cyclotron Research Center
Liège
Belgium

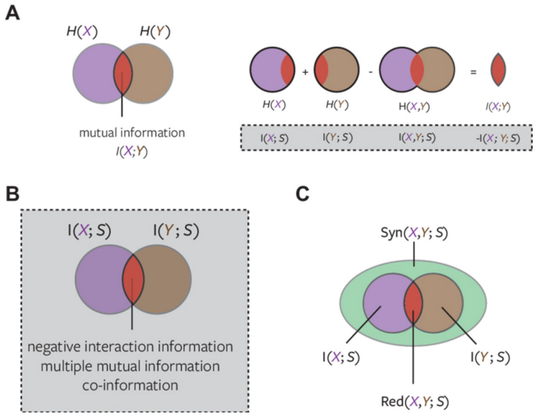
Monday, Jun 24: 3:15 PM - 4:30 PM
1749
Symposium
COEX
Room: Grand Ballroom 103

We are investigators from different disciplines, who use fMRI as a means to quantify different aspects of cognition and behavior. During the last year, we noticed that our independent studies using fMRI converged on a common topic, the Global Signal (GS). Indicatively, Prof. Uddin shows that the GS topography can be informative across the life span (Li, et al 2019; Nomi et al., 2023), Prof. Van De Ville indicates that GS can mathematically influence dynamic connectivity analyses (Van de Ville et al, 2019), Dr Mortaheb shows that the GS amplitude completes the interpretation of ongoing mental state reports (Mortaheb et al, 2022; 2023), and Prof. Liu's work on the GS aptly contextualizes this work (Liu et al, 2018). Coming together as a panel, we believe that we can provide an updated comprehensive discussion on where we stand methodologically and theoretically on the ongoing debate about the GS as a source of noise or of rich information.

Separating the effects of blood flow and global signal



Partial information decomposition

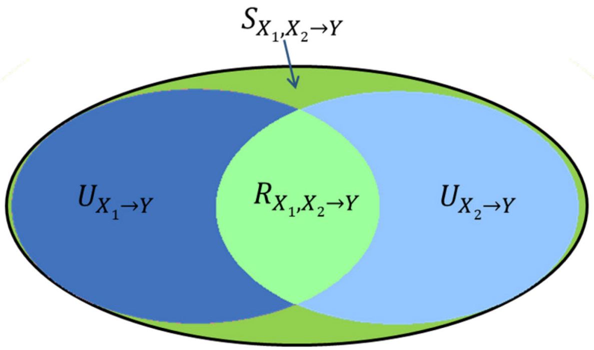


I(X;Y;Z)=

I(X;Y)-I(X;Y|Z) =

I(X;Z) + I(Y;Z) – I(X,Y;Z)

Invariant under permutations!



Distinct non-negative measures of redundancy and synergy, accounting for the possibility that redundancy and synergy may coexist as separate elements of information modification.

The interaction TE is actually a measure of the 'net' synergy manifested in the transfer of information from the two sources to the target.

$$TE_{X_1,X_2\to Y} = U_{X_1\to Y} + U_{X_2\to Y} + R_{X_1,X_2\to Y} + S_{X_1,X_2\to Y}$$

$$TE_{X_1\to Y} = U_{X_1\to Y} + R_{X_1,X_2\to Y}$$

$$TE_{X_2\to Y} = U_{X_2\to Y} + R_{X_1,X_2\to Y}$$

$$R_{X_1,X_2\to Y} = \min\{TE_{X_1\to Y}, TE_{X_2\to Y}\}$$

PID components cannot be obtained through classic information theory simply subtracting conditional MI terms: one more relation is needed. Shannon information theory does not univocally determine this decomposition

Redundancy can be defined as the minimum of the information provided by each individual source to the target (other recipes exist)

This choice satisfies the desirable property that the redundant TE is independent of the correlation between the source processes.

Multiscale Information Decomposition: Exact Computation for Multivariate Gaussian Processes

by Luca Faes [1,2,*], Daniele Marinazzo [3] and Sebastiano Stramaglia [4,5]

1 Bruno Kessler Foundation, 38123 Trento, Italy
2 BIOtech, Department of Industrial Engineering, University of Trento, 38123 Trento, Italy
3 Data Analysis Department, Ghent University, 9000 Ghent, Belgium
4 Dipartimento di Fisica, Universitá degli Studi Aldo Moro, 70126 Bari, Italy
5 Istituto Nazionale di Fisica Nucleare, 70126 Sezione di Bari, Italy
* Author to whom correspondence should be addressed.

Entropy **2017**, *19*(8), 408; https://doi.org/10.3390/e19080408

P. Williams and R. D. Beer. "Nonnegative decomposition of multivariate information." arXiv preprint arXiv:1004.2515 (2010).

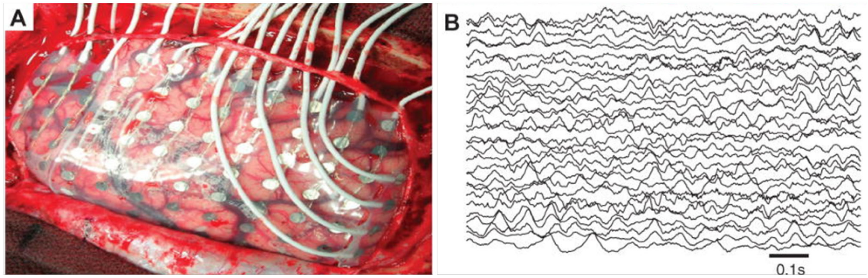
PID is particularly relevant when some signals are very similar

PID vs IID on similar signals

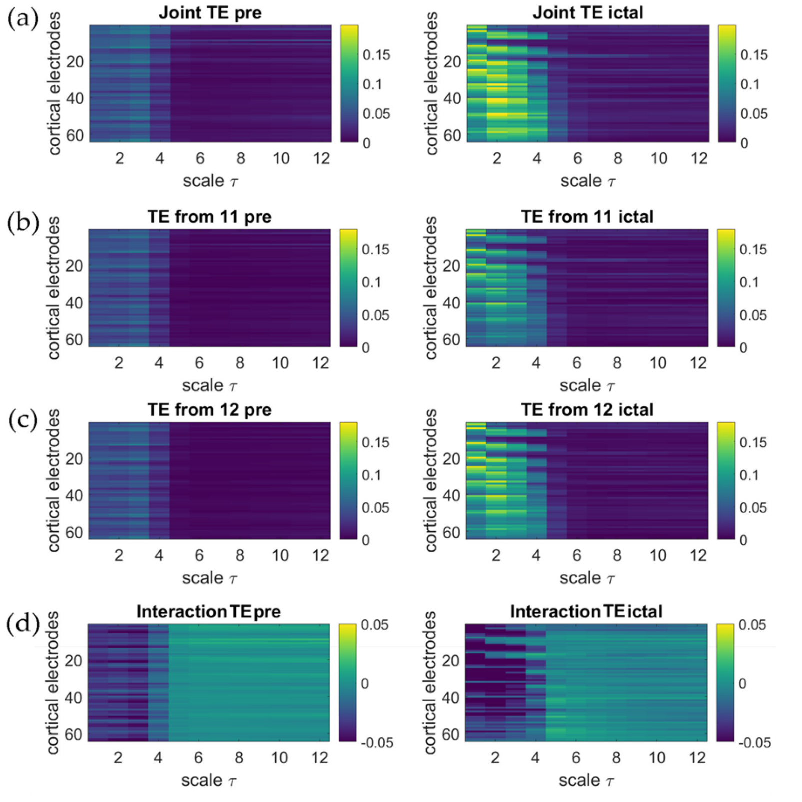
We look at 64 cortical electrodes as targets, and two depth hippocampal electrodes (11 and 12) as drivers

Multiscale Information Decomposition: Exact Computation for Multivariate Gaussian Processes

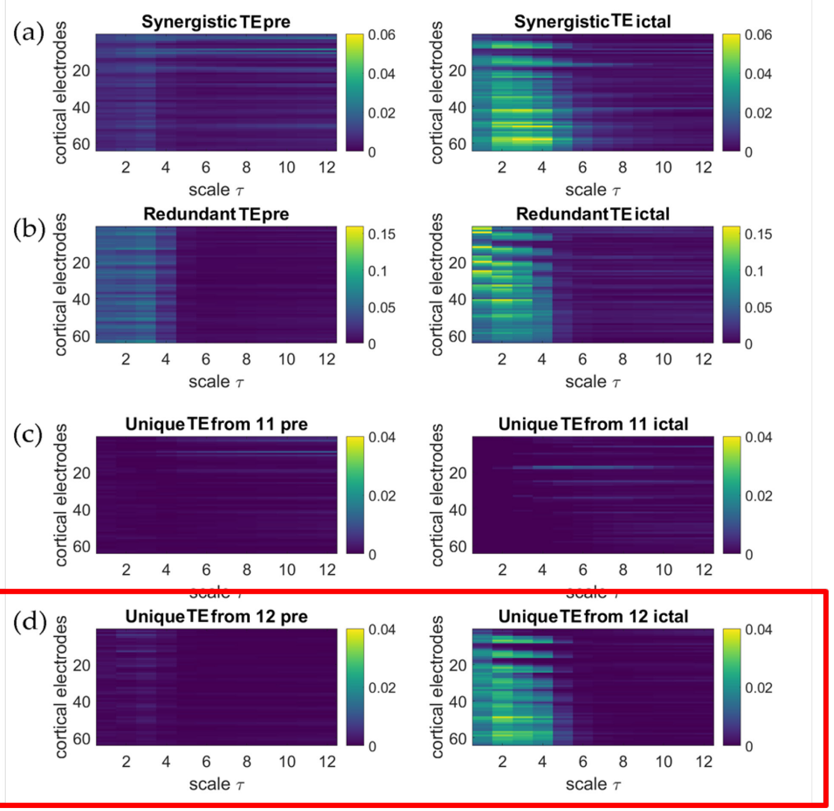
by Luca Faes [1,2,*], Daniele Marinazzo [3] and Sebastiano Stramaglia [4,5]

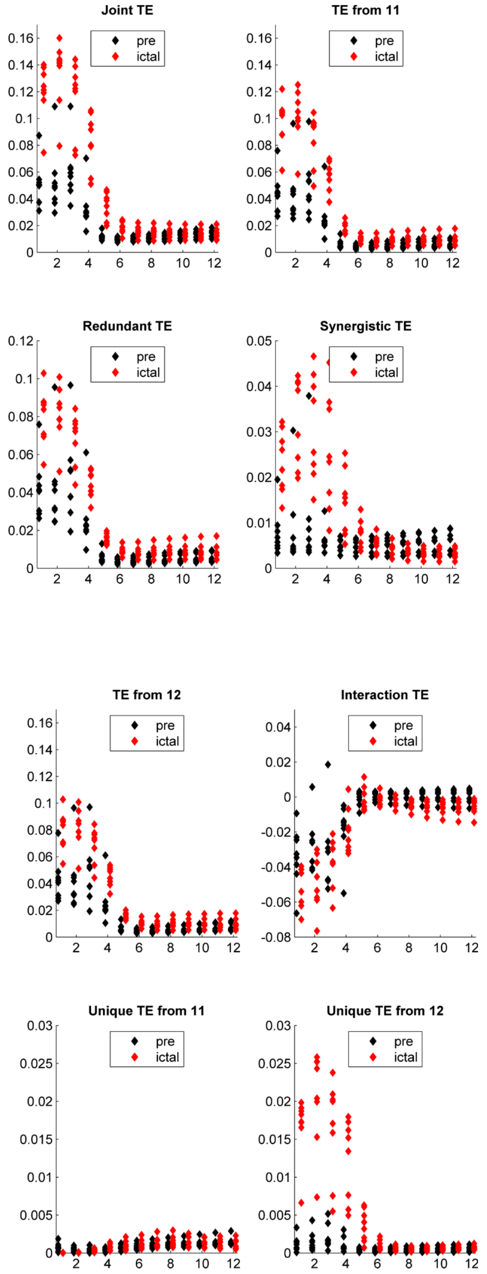


Interaction Information Decomposition (IID)

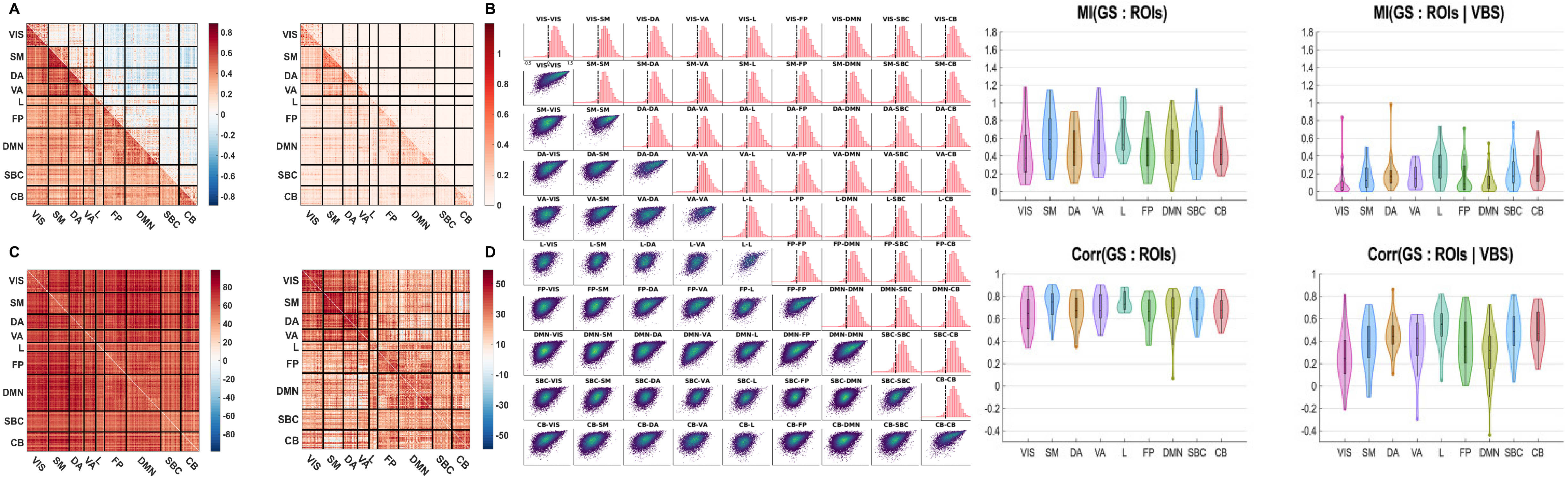


Partial Information Decomposition (PID)

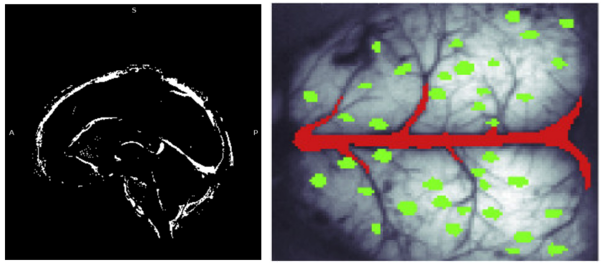




Differential network effect of GSR



Investigate the JOINT role of Global Signal and BOLD from vessels towards the different regions in the brain using the framework of Multiscale Partial Information Decomposition, using simultaneous calcium and BOLD recordings in a mouse as a control

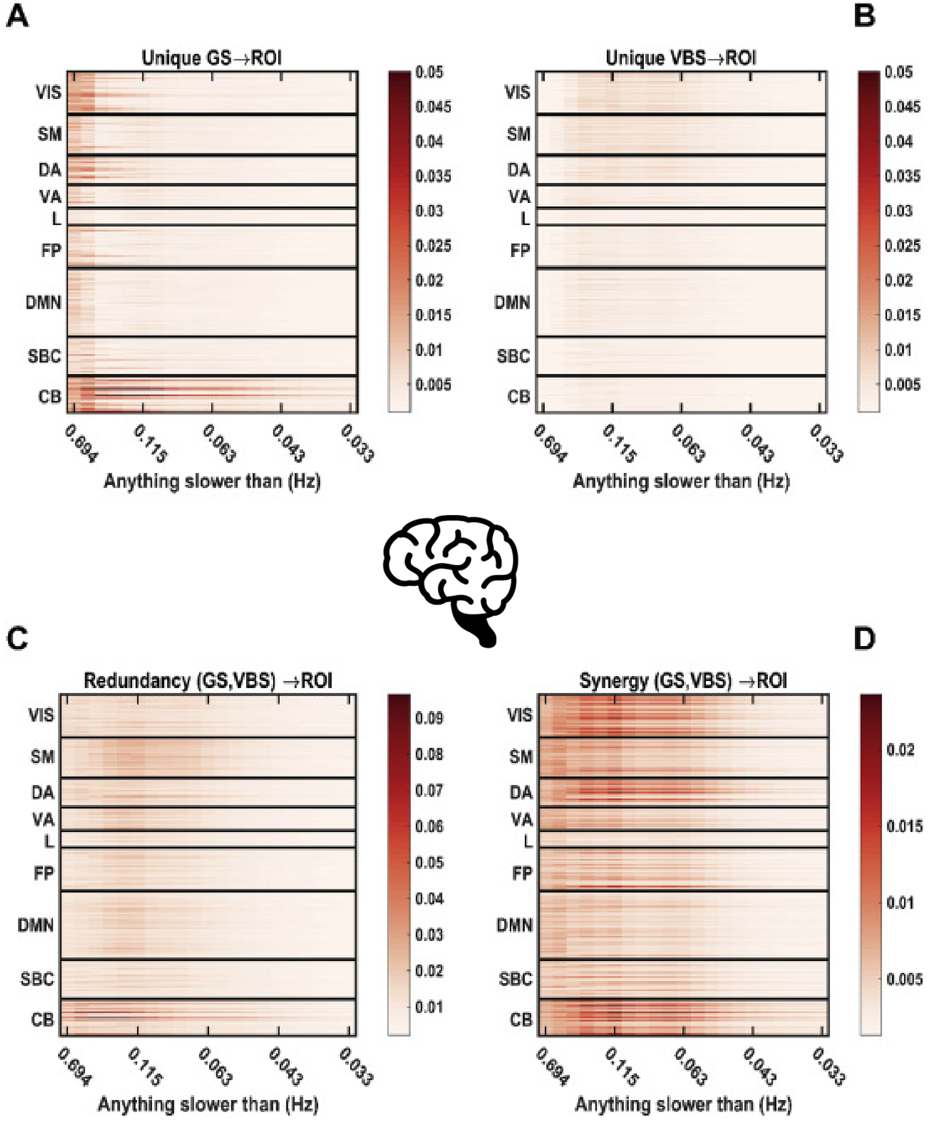


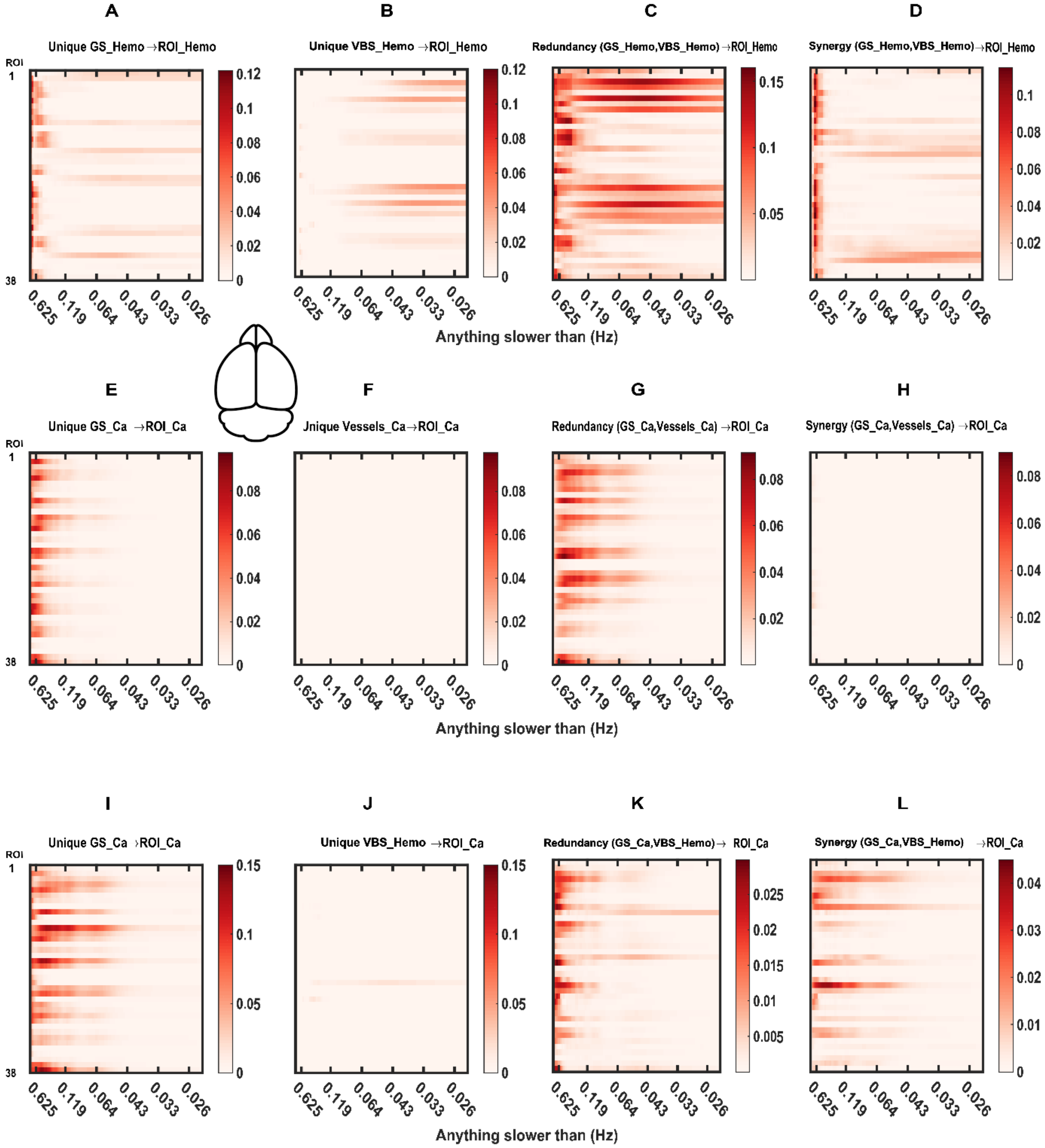
ELSEVIER
NeuroImage
Volume 213, June 2020, 116699

Disambiguating the role of blood flow and global signal with partial information decomposition

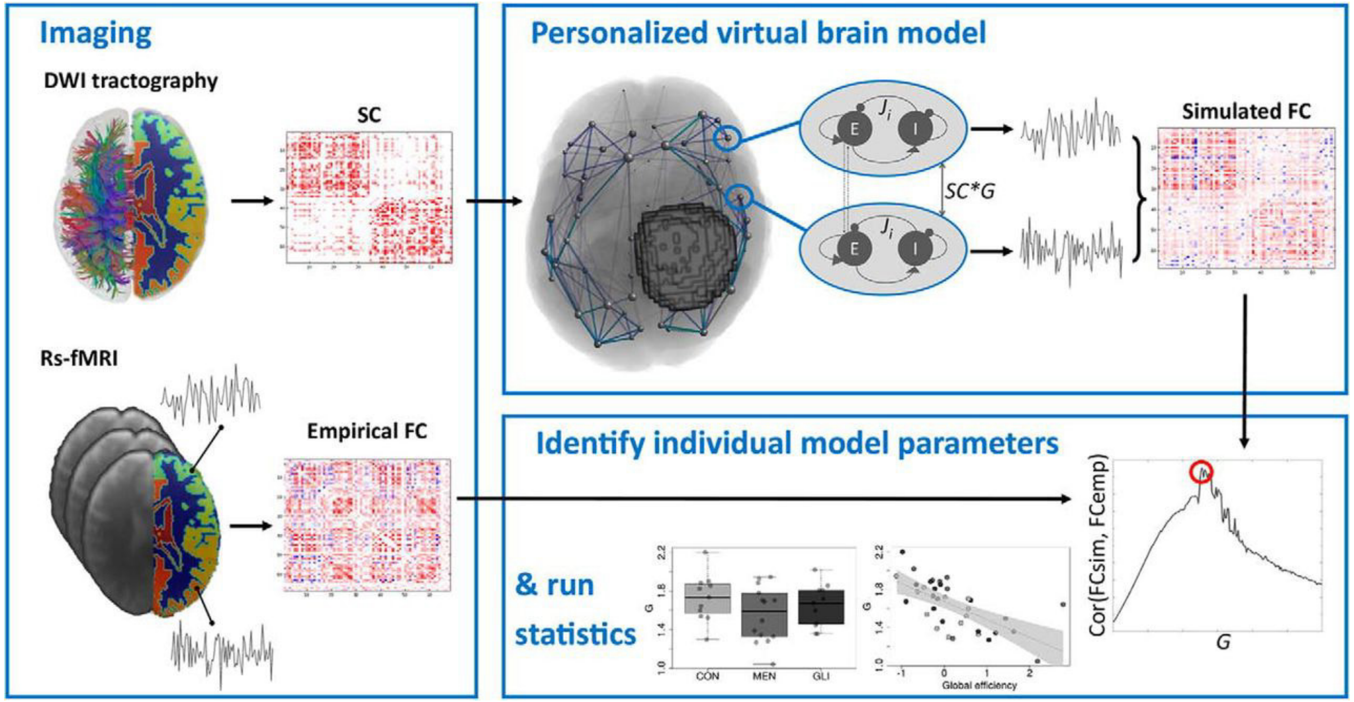
Nigel Colenbier [a], Frederik Van de Steen [a], Lucina Q. Uddin [b], Russell A. Poldrack [c], Vince D. Calhoun [d, e], Daniele Marinazzo [a]

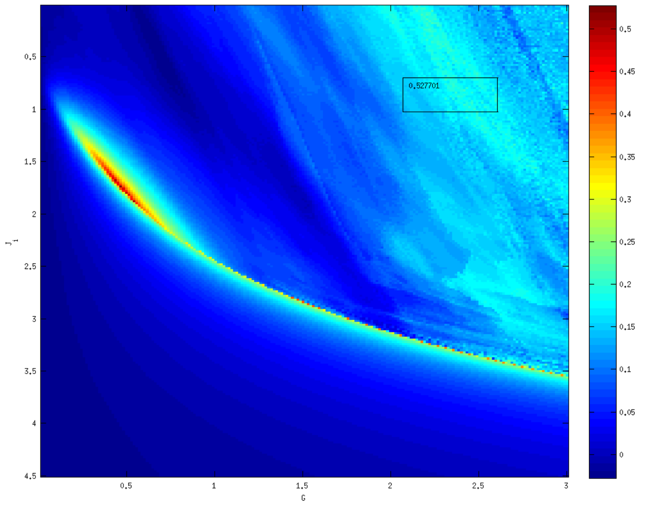
PID (GS,Vessels->ROI)

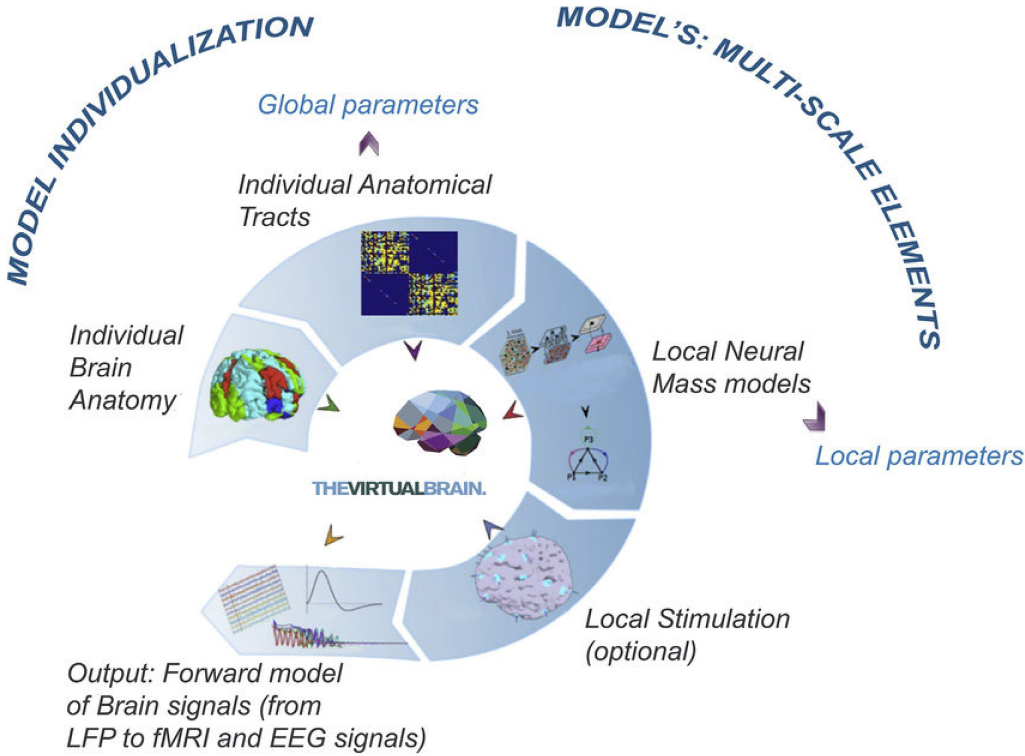




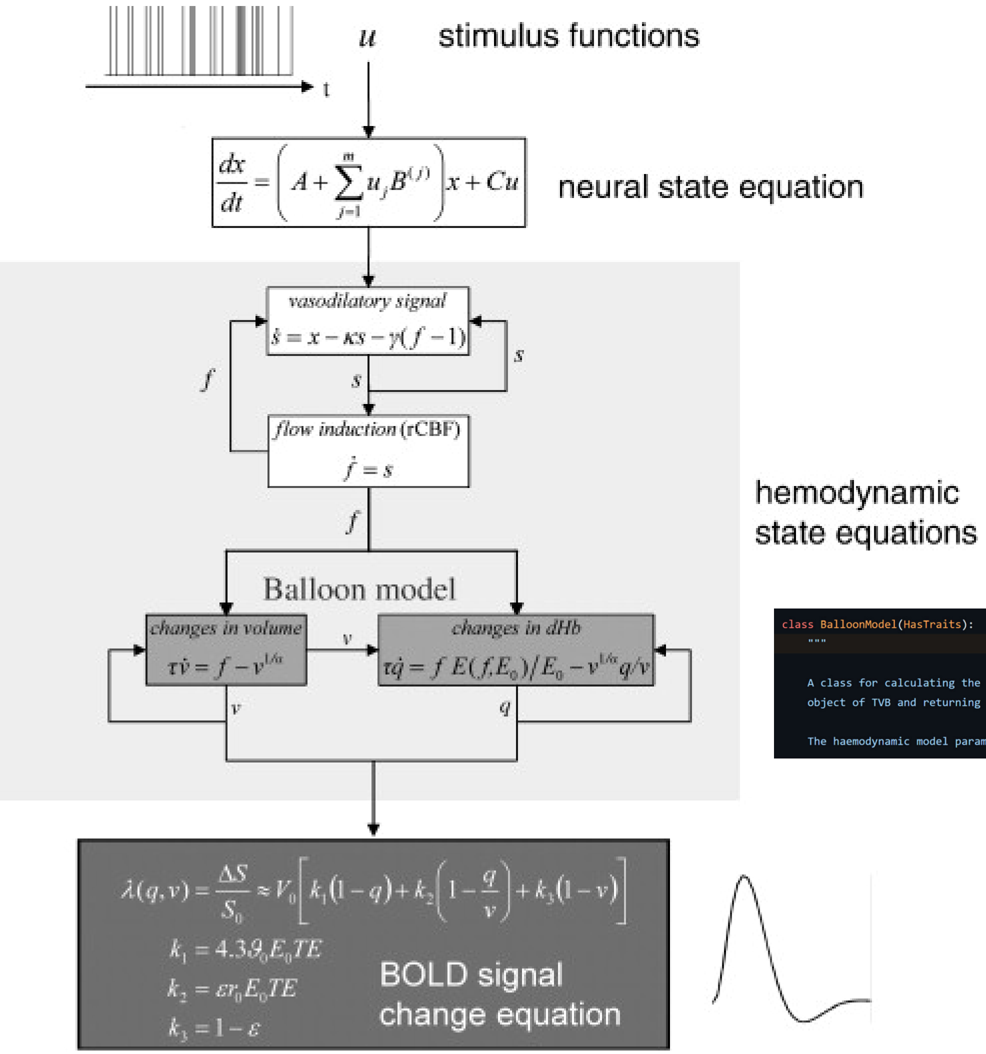
The standard way to simulate fMRI data with TVB







Hemodynamics is “modelled” but only as a filter



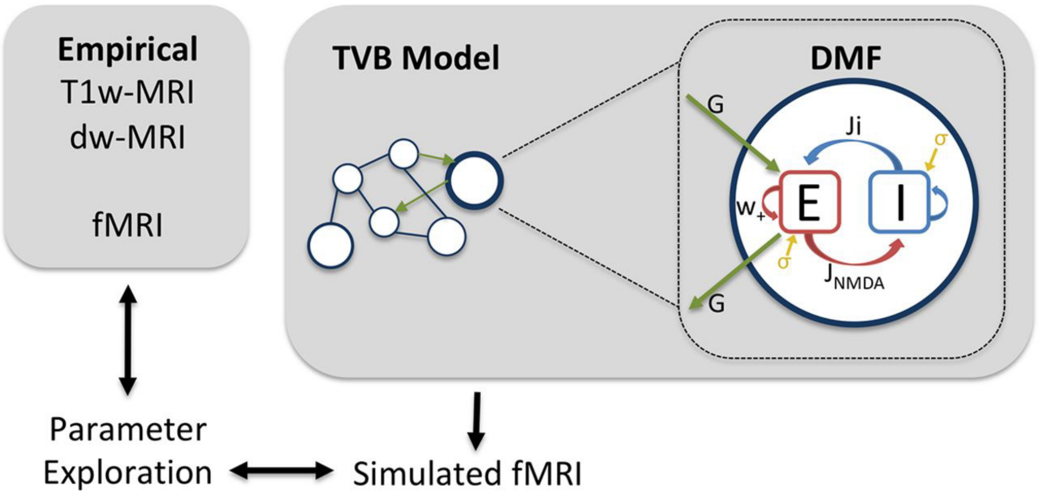
Stephan et al. Neuroimage 2007

```
class BalloonModel(HasTraits):
    """

    A class for calculating the simulated BOLD signal given a TimeSeries
    object of TVB and returning another TimeSeries object.

    The haemodynamic model parameters based on constants for a 1.5 T scanner.
```

that represents the connections strength, and three synaptic parameters, i.e., the excitatory (NMDA) synapses (J_{NMDA}), the inhibitory (GABA) synapses (J_i), and the recurrent excitation (w_+). The neural activity simulated with TVB was fed into the Balloon-Windkessel hemodynamic model (Stephan et al., 2007) to reconstruct resting-state BOLD fMRI time-courses over 8 min length and compute simulated FC (simFC) and FCD (simFCD). Parameters were adjusted

data, respectively. Each subject's unique structural connectome constrained their personal brain simulation, wherei local dynamics were represented by the dynamic mean field (DMF) model (**Eqs. 1–6**; **Deco et al., 2014a,b**). The simulated local synaptic gating potentials were then fed through the Balloon–Windkessel hemodynamic model, producing simulated fMRI time series. Each subject's simulated fMRI time series was fitted to their functional

sampling frequency $f_s = 100$ Hz. The time step was variable to adapt the integration process and avoid numerical errors or instabilities and the neural mass field was filtered via the Balloon-Windkessel model (Fristonetal., 2000) to emulate fMRI time series with repetition time TR set to 2000ms.



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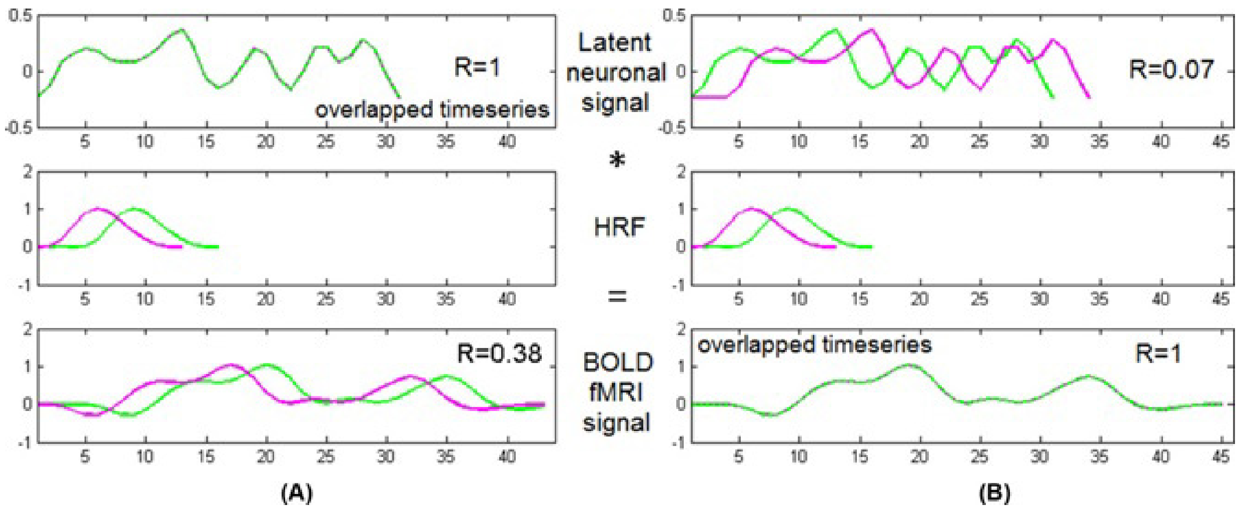
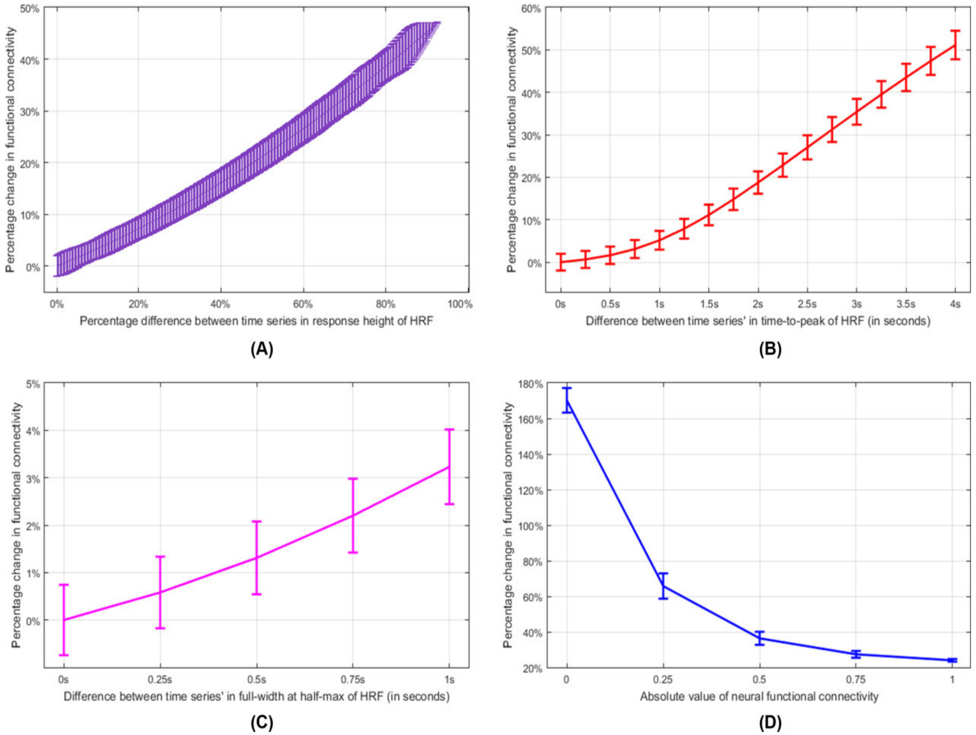
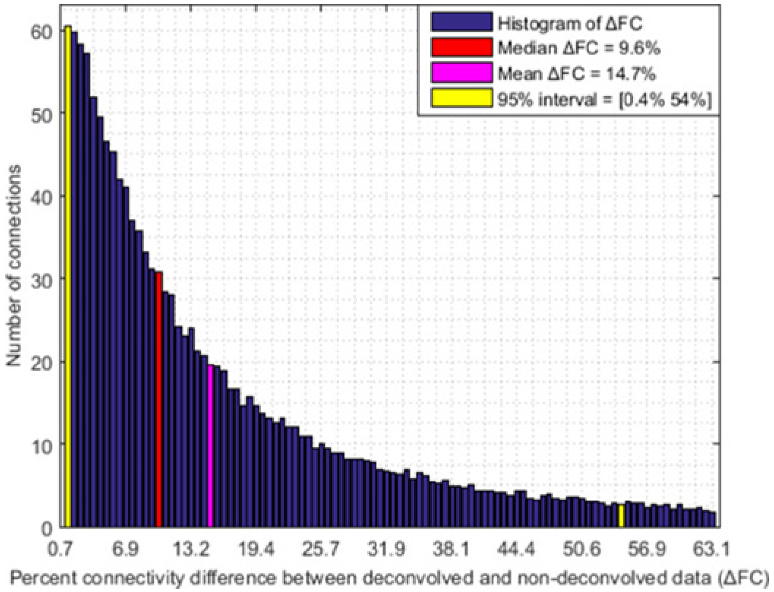
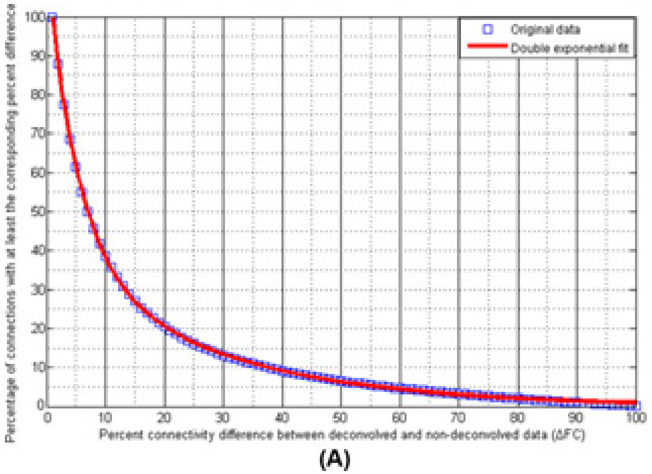
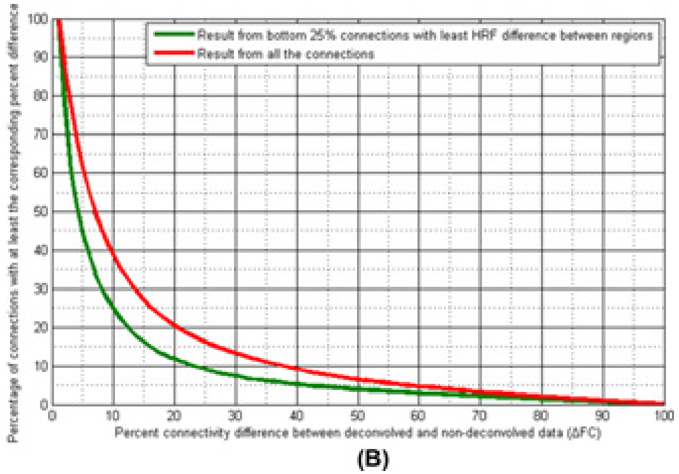
Effect of HRF variability on functional connectivity











EBRAINS 2.0

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How to address these issues in whole-brain modelling?

- *Simulate all physiology and physiological interactions*
- Use a region- and subject-specific retrieved HRF
- Use physiological variables as covariates/regressors in statistical analyses
- Consider blood arrival time across brain regions

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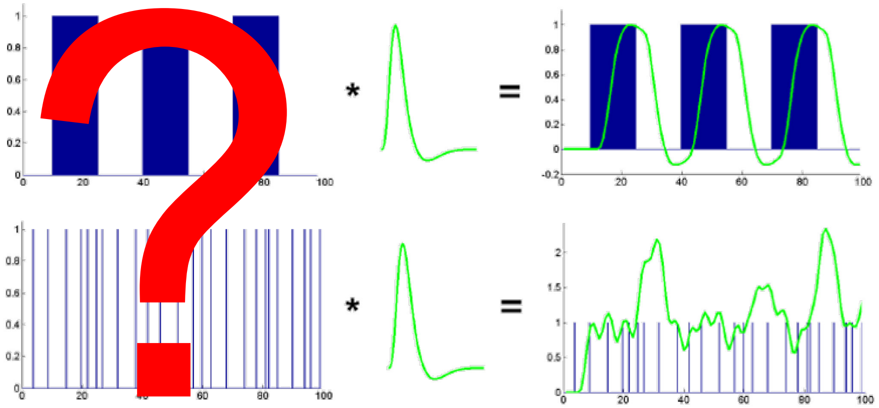
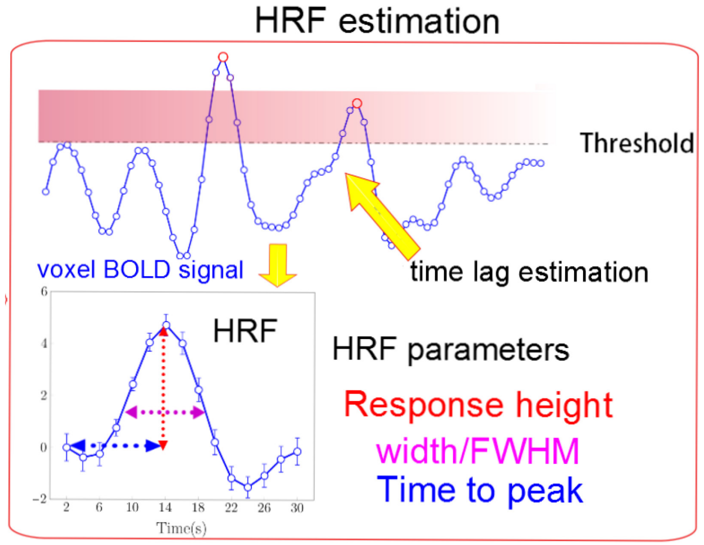
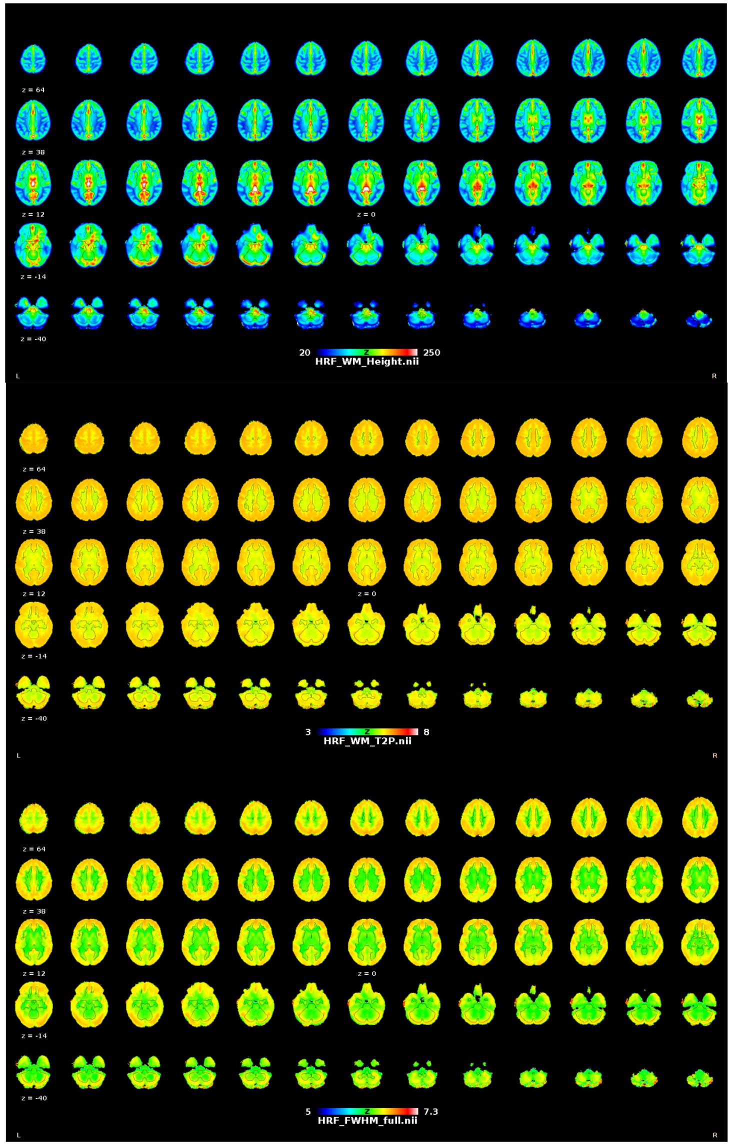
Estimate voxel- and subject-specific HRF from resting state BOLD







regression model for a single voxel (i):

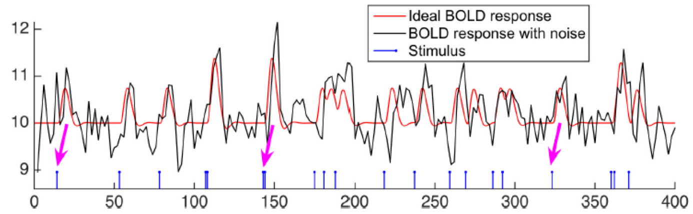
$$y_i = \beta_0 + \beta_1 x_{1i} + \ldots + \epsilon_i$$

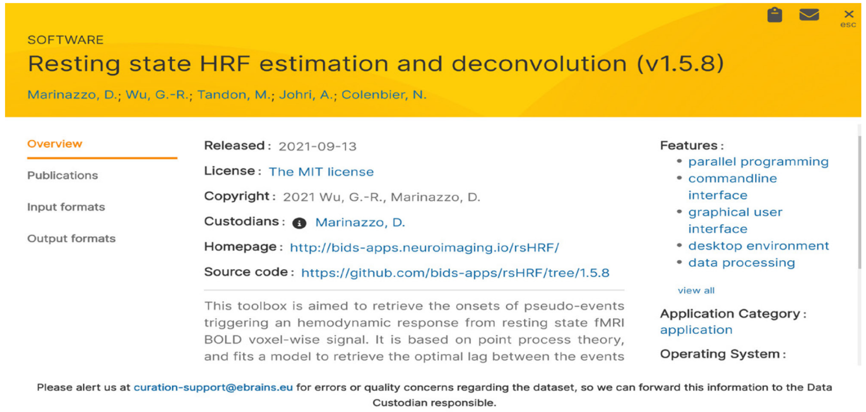
or in words:

$$(\text{voxel activity}) = \text{baseline} + \beta_1 \times (\text{timing information}) + \ldots + \text{error}$$

From neuronal pseudo-events to BOLD peaks

we assume the peak of BOLD response lags behind the peak of spontaneous point process event is $L = \kappa \cdot TR/N$ seconds (0 <L <PST).





SOFTWARE

Resting state HRF estimation and deconvolution (v1.5.8)

Marinazzo, D.; Wu, G.-R.; Tandon, M.; Johri, A.; Colenbier, N.

Overview
Publications
Input formats
Output formats

Released: 2021-09-13
License: The MIT license
Copyright: 2021 Wu, G.-R., Marinazzo, D.
Custodians: Marinazzo, D.
Homepage: http://bids-apps.neuroimaging.io/rsHRF/
Source code: https://github.com/bids-apps/rsHRF/tree/1.5.8

This toolbox is aimed to retrieve the onsets of pseudo-events triggering an hemodynamic response from resting state fMRI BOLD voxel-wise signal. It is based on point process theory, and fits a model to retrieve the optimal lag between the events

Features:
- parallel programming
- commandline interface
- graphical user interface
- desktop environment
- data processing

view all

Application Category: application

Operating System:

Please alert us at curation-support@ebrains.eu for errors or quality concerns regarding the dataset, so we can forward this information to the Data Custodian responsible.

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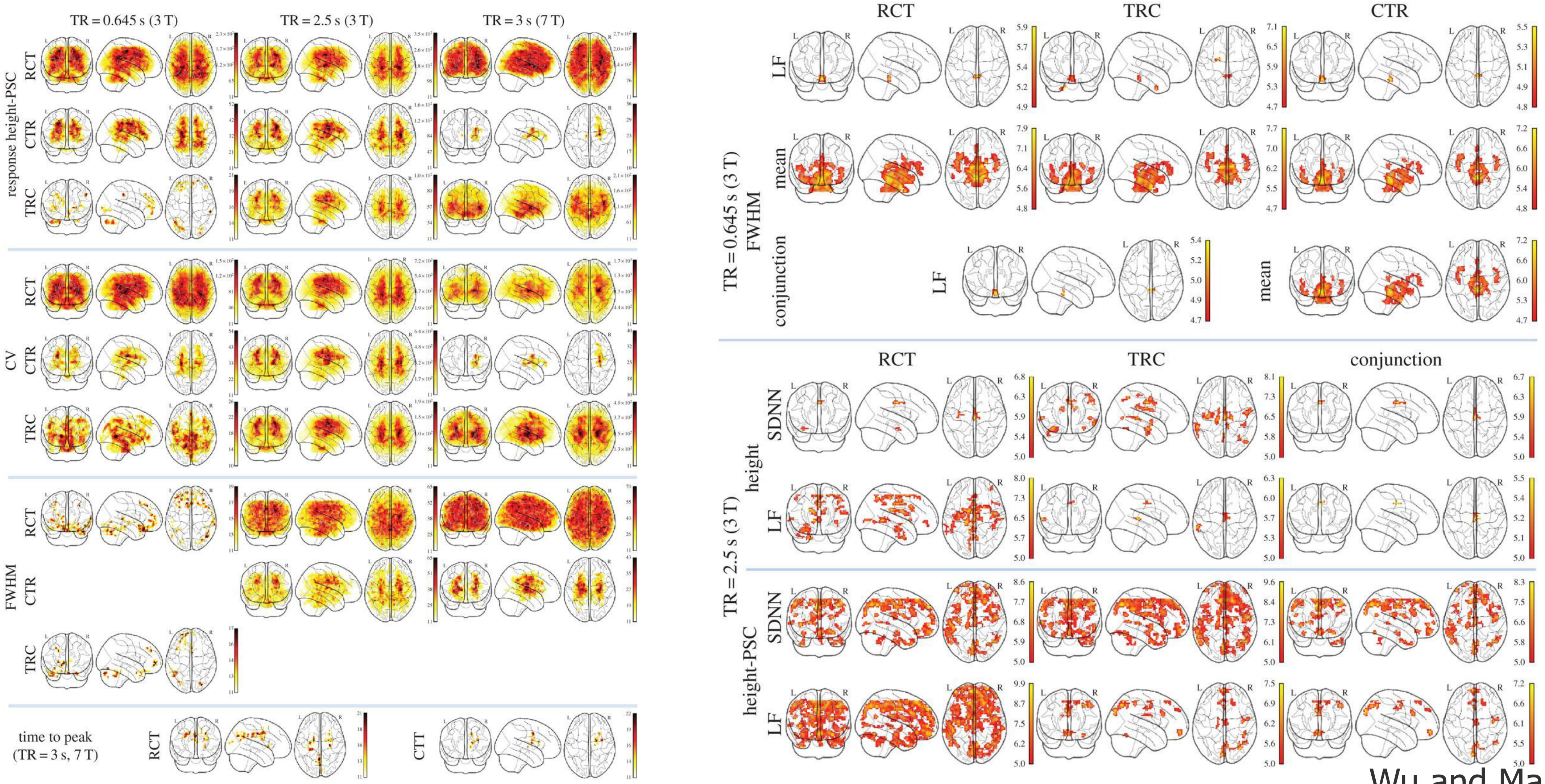
Processing steps and order impact HRF estimation and correlation with heart rate variability

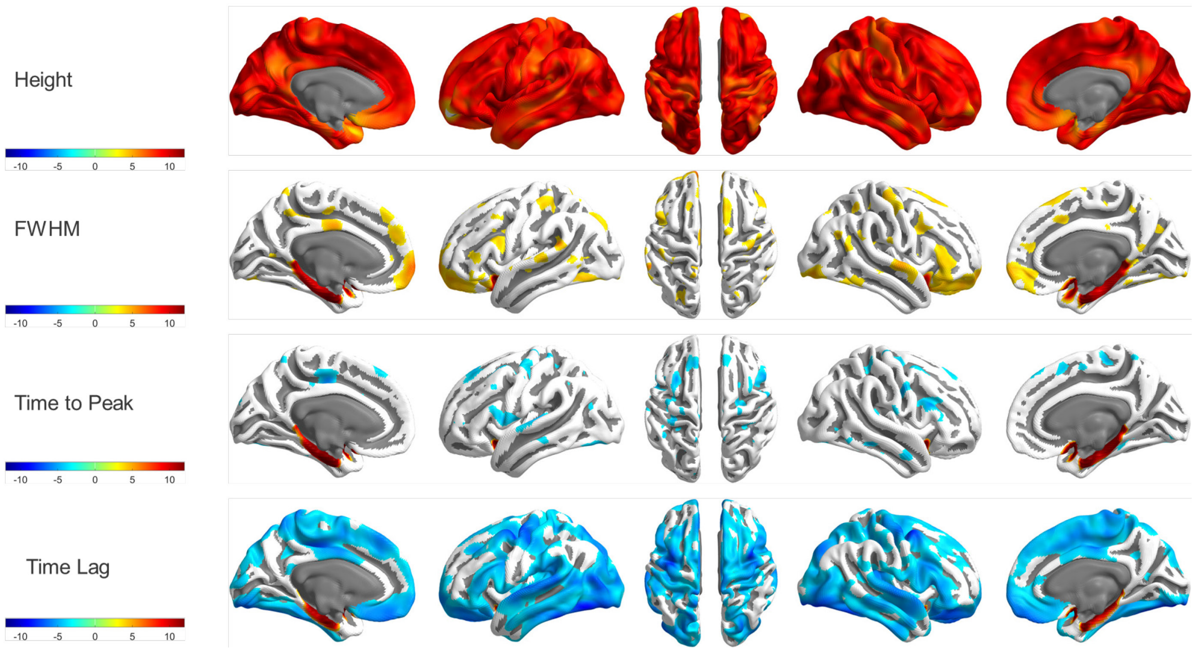
slice timing correction (T), registration (R), physiological correction (C), despiking (D), and normalization (N).



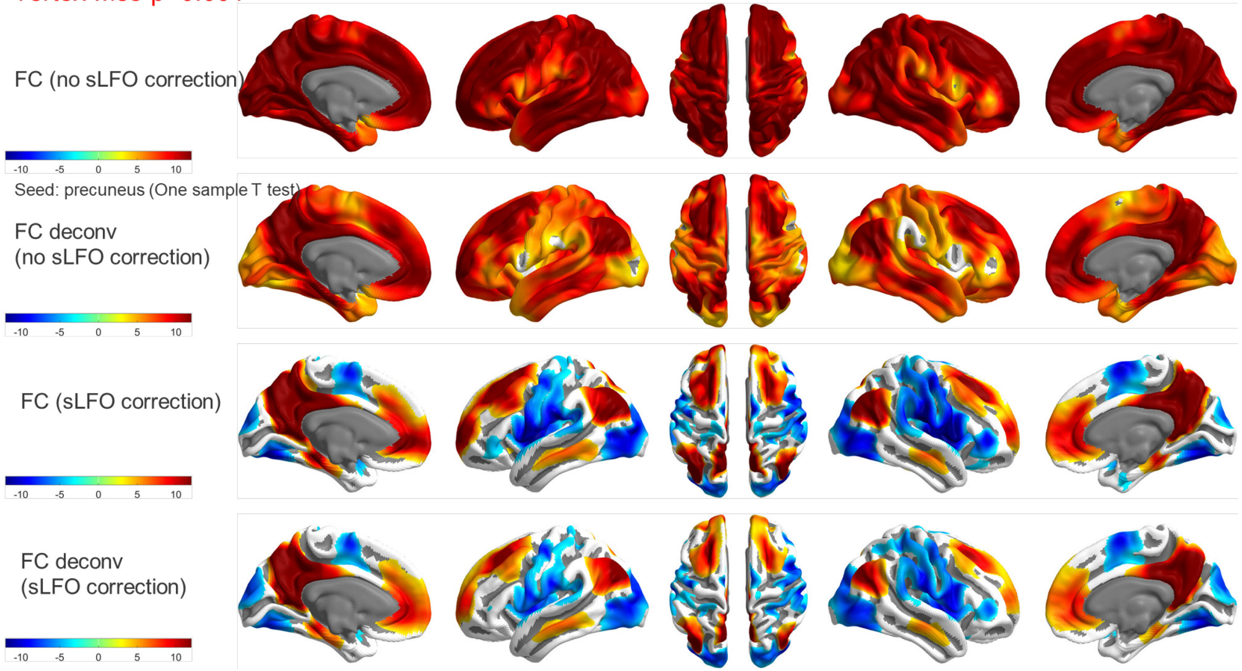
Wu and Marinazzo 2016

Rapidtide sLFO correction impacts HRF shape and FC

vertex wise p<0.001(Paired t-Test: no sLFO correction – sLFO correction)



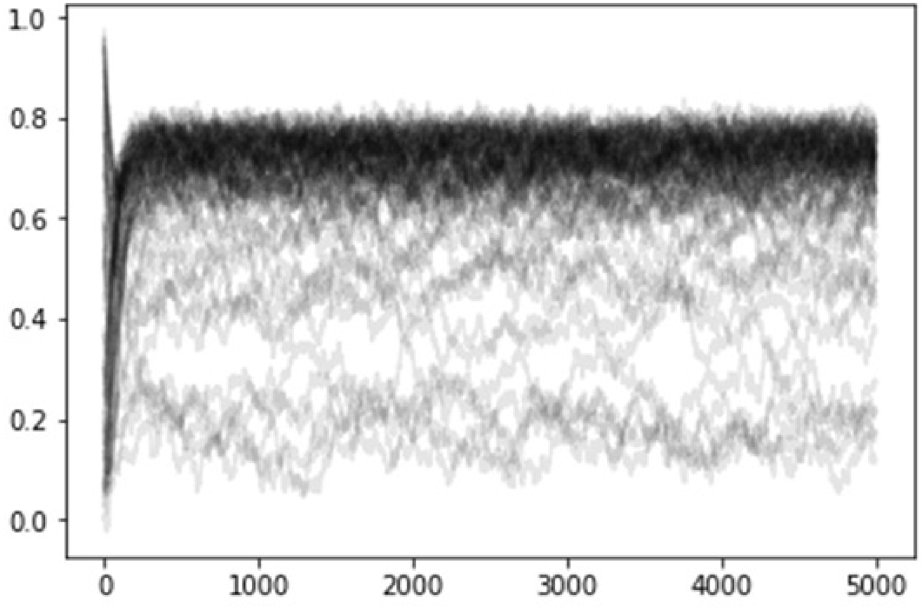
vertex wise p<0.001



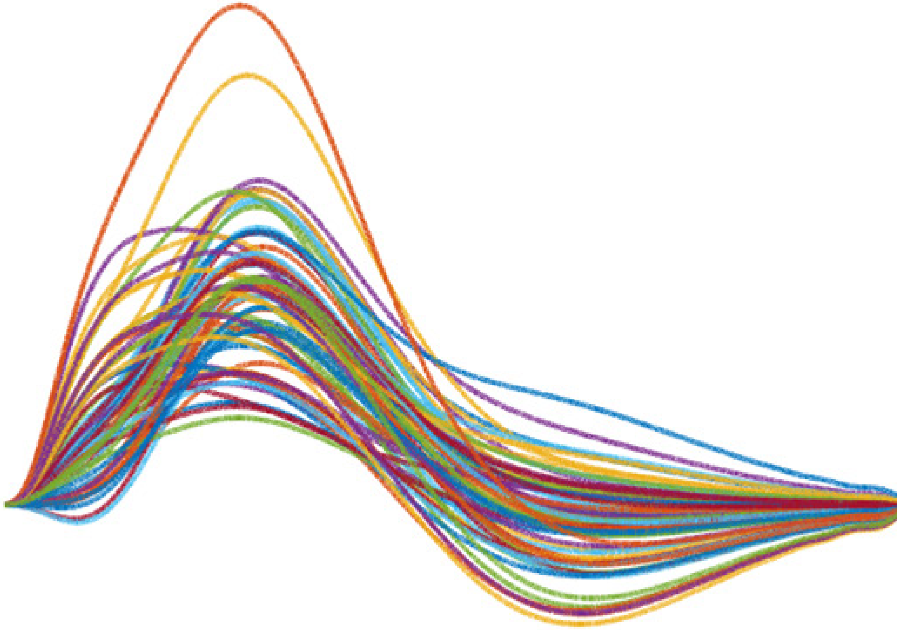
Region- and subject-specific HRF in TVB

For every value in the parameter space exploration

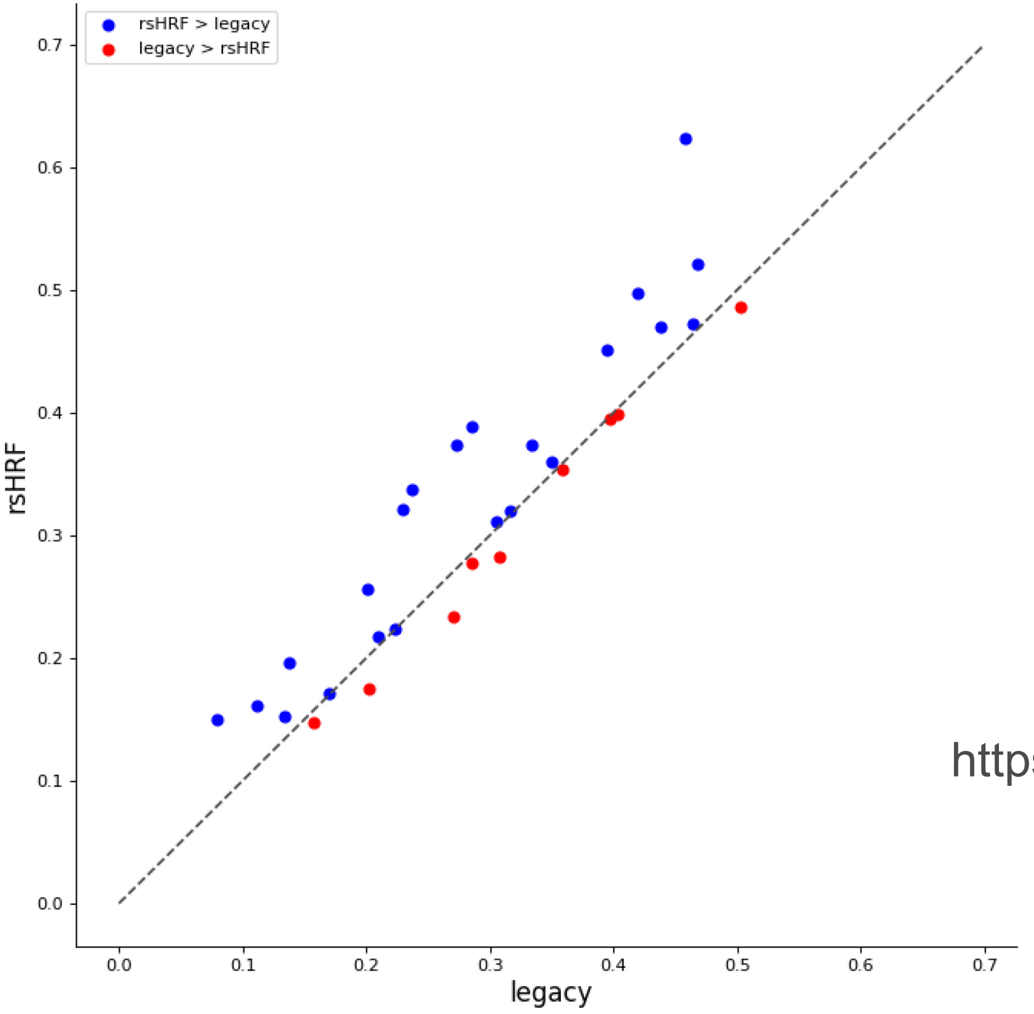
- Obtain the non-averaged (raw) synaptic gating activity with the Wong-Wang model
- ~~Legacy TVB: Map to BOLD through a Balloon-Windkessel model of the HRF~~
- Convolve with personalized region specific HRF, upsampled to model time scale
- Downsample to empirical BOLD
- Obtain simulated FC and compare to empirical FC

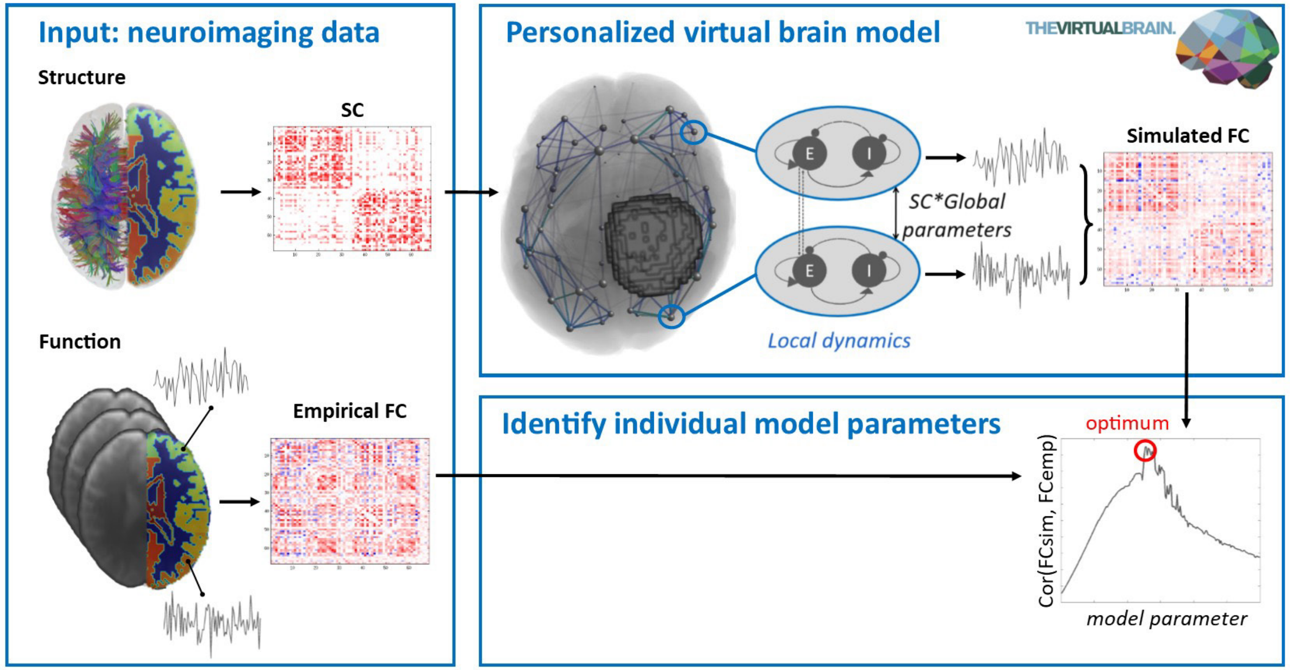


*



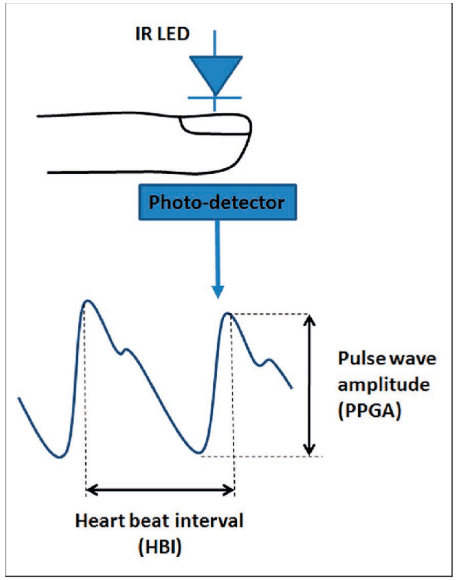
Personalized HRF increases similarity between empirical and simulated FC in a brain tumor fMRI+diffusion dataset



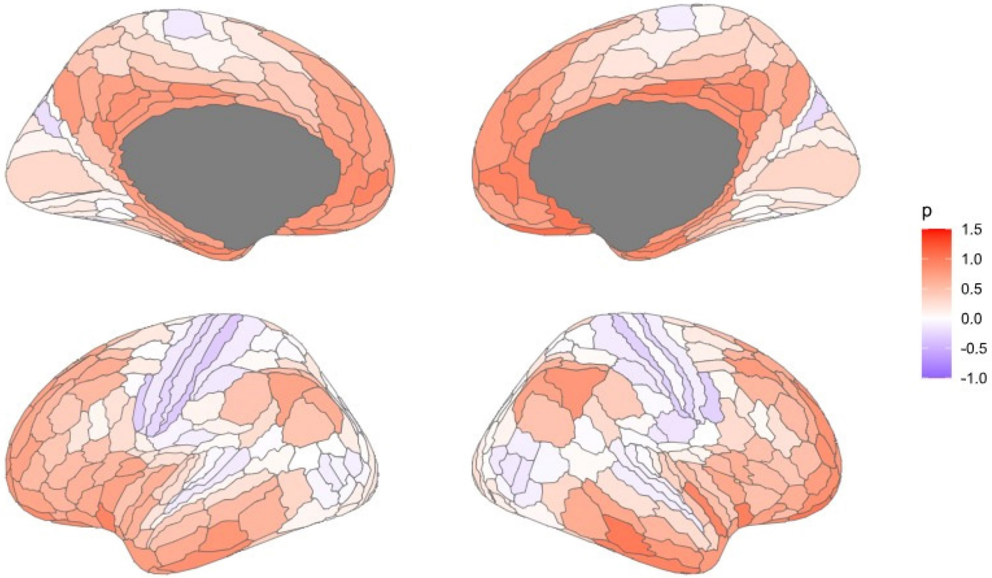


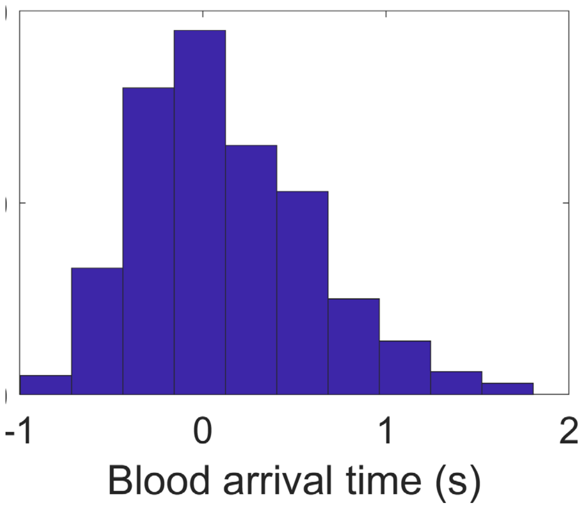
https://github.com/AmoghJohri/TVB-Tests/blob/master/REPORT.md

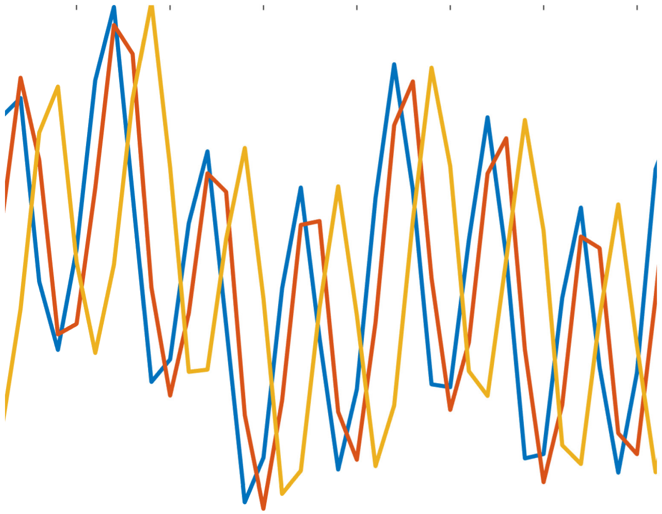
FC from simulation vs FC from delayed copies of the PPU signal (but it could be a completely fake signal FWIW)

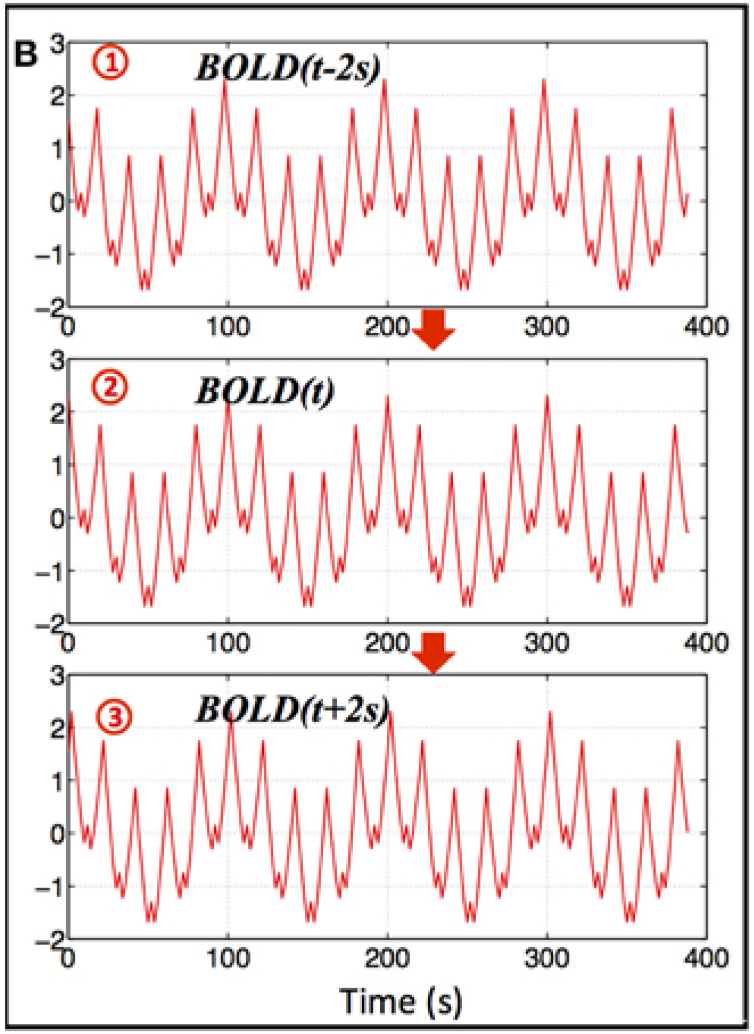


Glasser : Blood arrival time (690 subjects)



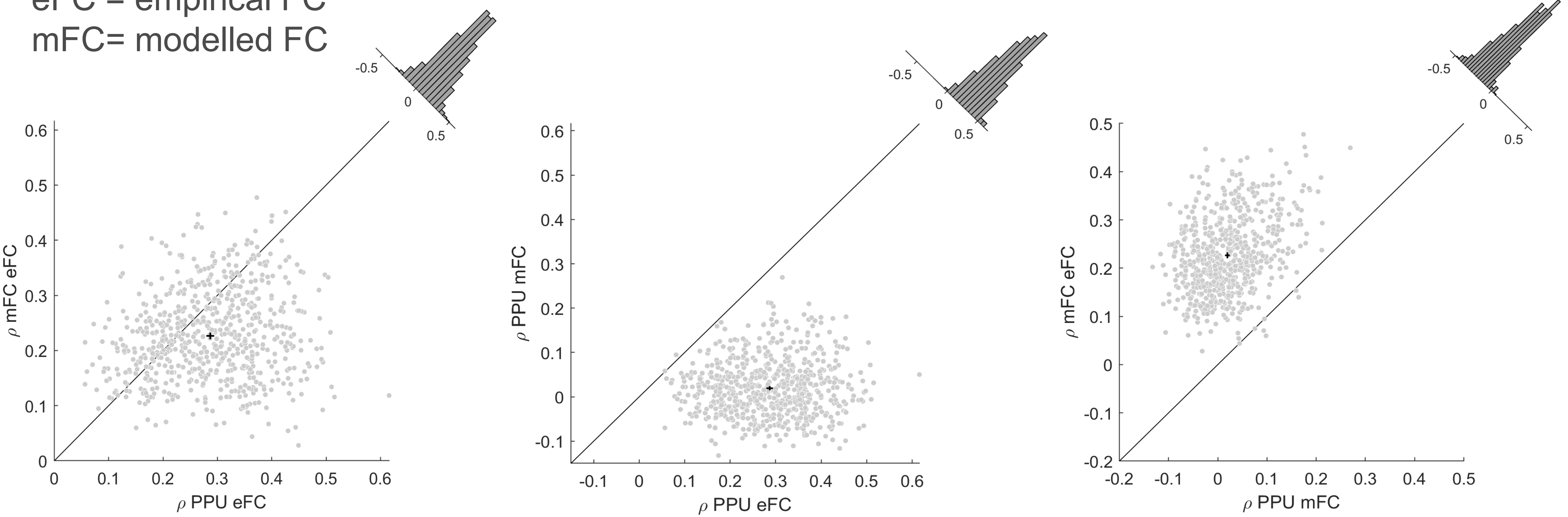






Correlations between differently obtained FC matrices

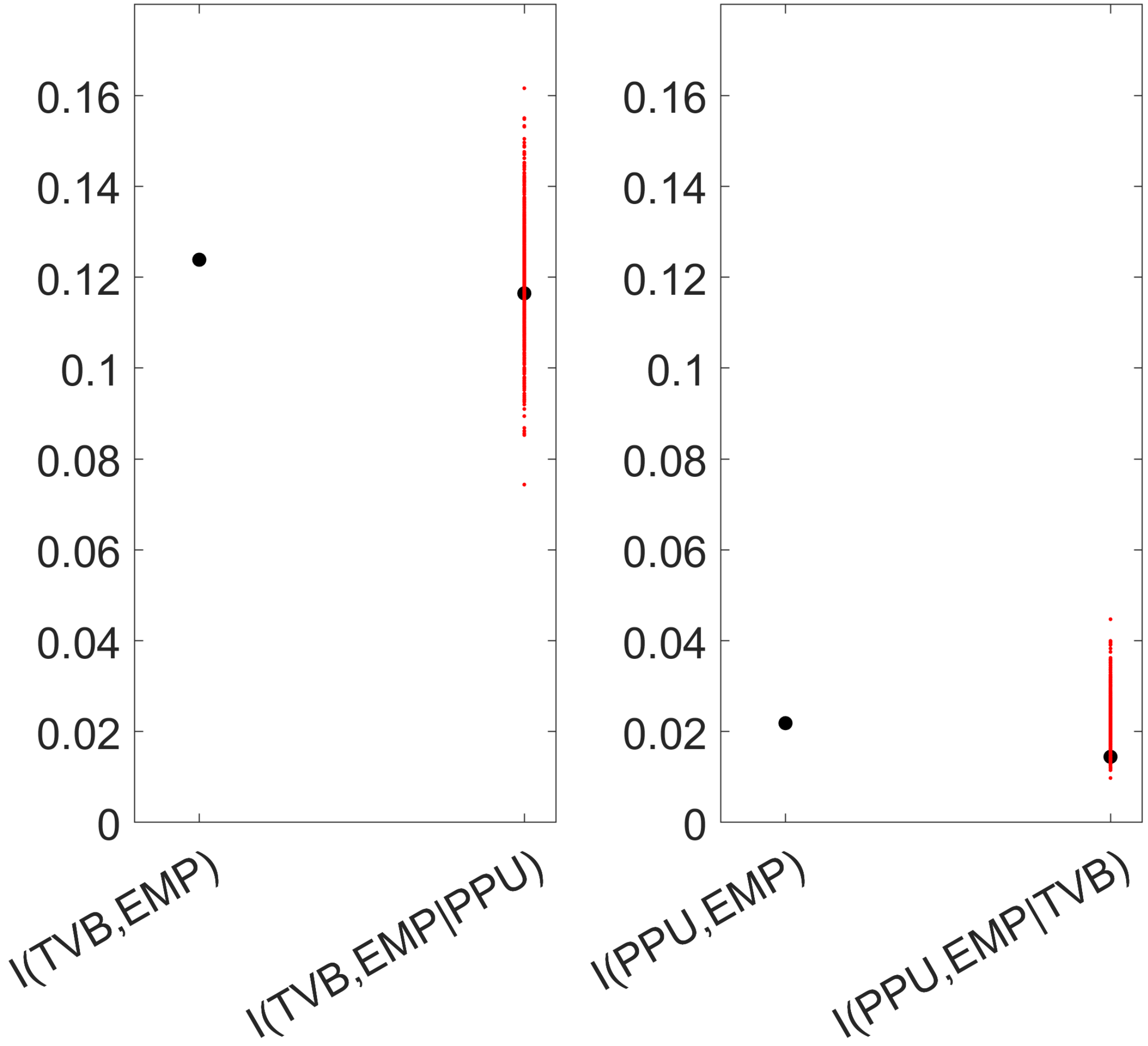
PPU = PP signal delayed according to BAT
eFC = empirical FC
mFC= modelled FC



Delayed PP produces a FC which is slightly more correlated with the empirical FC wrt the legacy TVB model

PP-FC is unrelated to TVB model of FC

No significant interaction effects

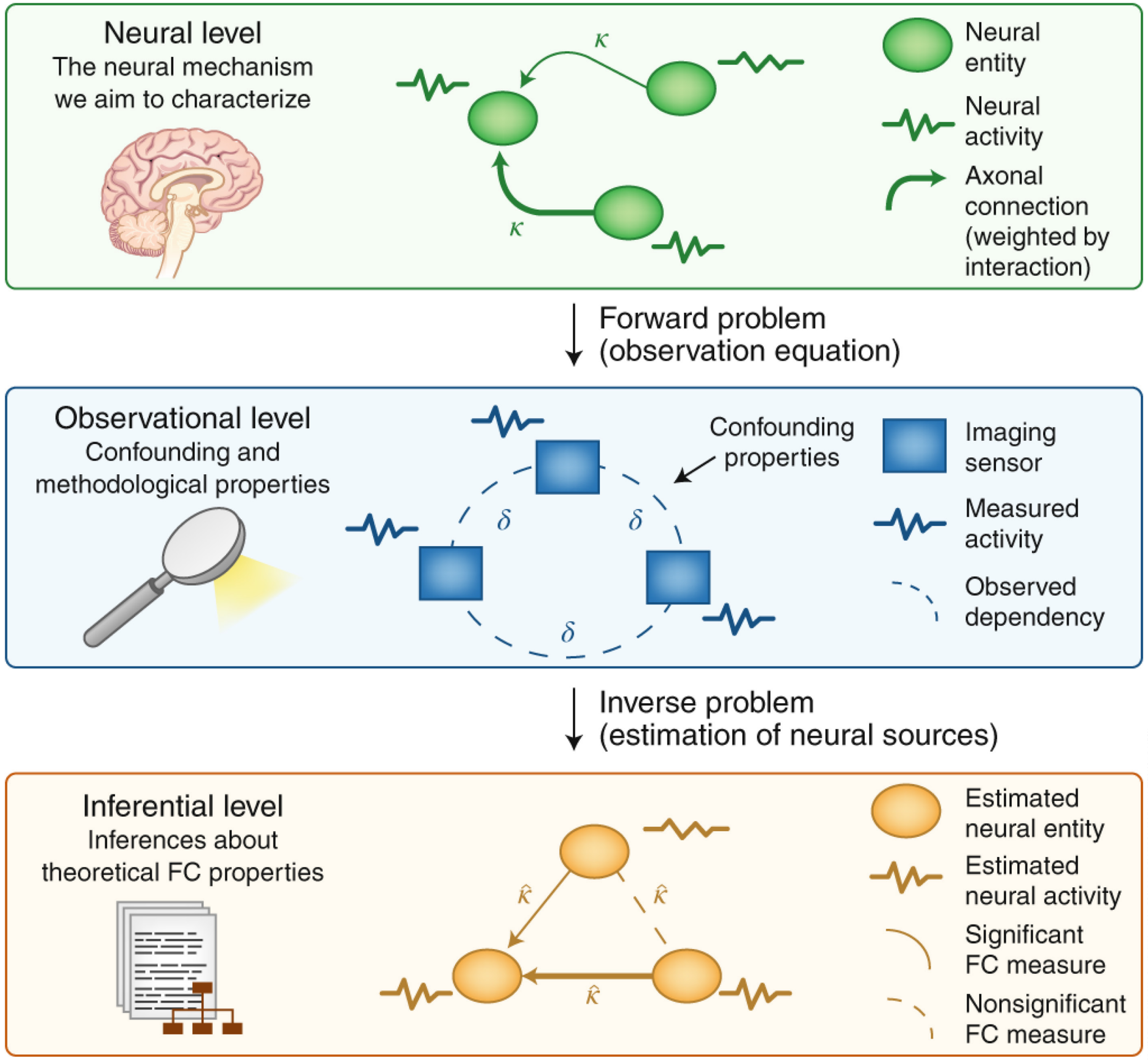


LETTER | OPEN ACCESS

Disentangling high-order effects in the transfer entropy

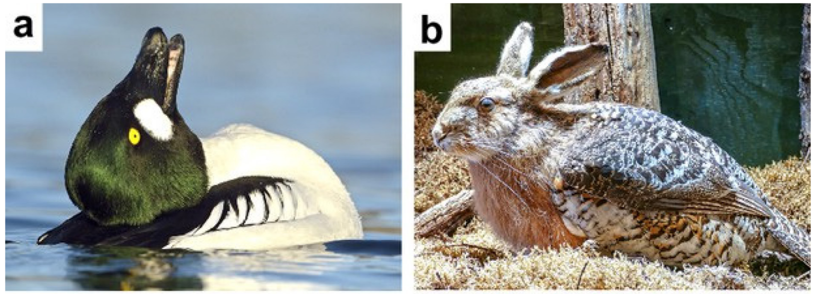
Sebastiano Stramaglia[1], Luca Faes[2], Jesus M. Cortes[3,4,5,6], and Daniele Marinazzo[7]

So what?



Reid et al. 2019

- Don’t forget that we’re working in a causal and inferential framework
- In a state space we cannot neglect transfer functions
- Physiology and hemodynamics are non-negligible data features.
- Blood arrival time produces a FC matrix which is as similar to the empirical FC as the one obtained by simulated BOLD data according to empirical SC and biologically inspired model.
- Is this super bad? No, this simply means that all these factors contribute, in a complementary way. And there definitely is a (causal) link between plumbing and neuronal activity in the brain. Still, modulations to FC are certainly also due to modulations in vascularization.
- Keep in mind which empirical FC connectivity matrix are you fitting: physiology and our clumsy strategies to handle it will definitely transform it.
- Maybe fit some data feature other than FC matrix.



Rubinov 2023

Co-funded by the European Union

EBRAINS 2.0

Thank you

daniele.marinazzo@ugent.be

Co-funded by the European Union

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