

Controversies, Mysteries, and Challenges of fMRI

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SFIM



FMRI

What Moves the Field of fMRI Forward?

The understanding that improvements in fMRI **sensitivity, speed, precision, ,information content, repeatability, interpretability** increase **utility**.

Individual: Curiosity, Ambition, Professional Stability/Promotion, Funding.

Institutional: Funding, Thematic Category

Research Community: Meetings, Workshops, Collaborations, Standardized Tools, Standardized Procedures, New Tools, New Platforms for creating/testing tools, vendor attention.

Neuroscience: Gaps in what we can measure and infer.

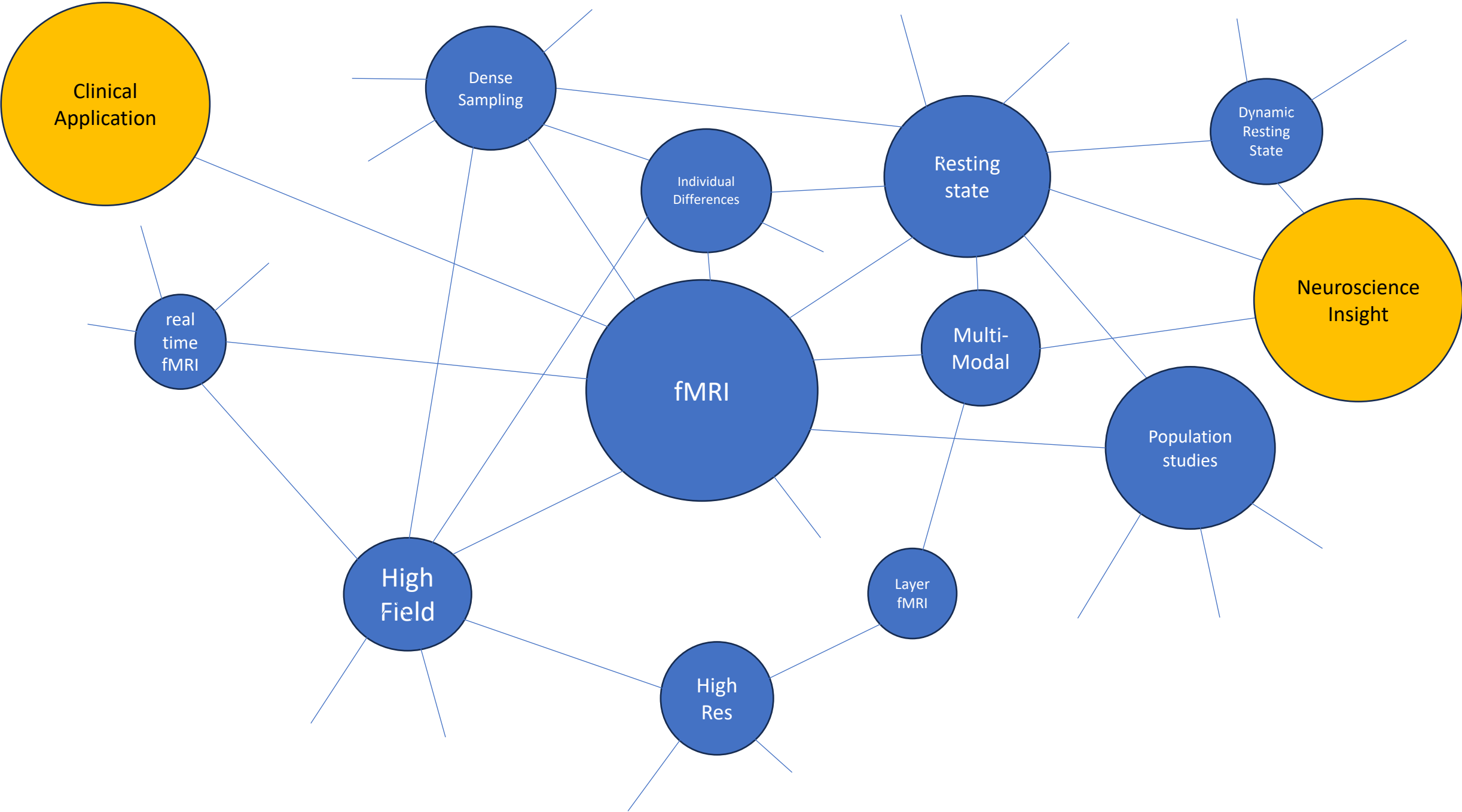
Clinical: Gaps in what measures can help diagnoses and treatment, cost effectiveness vs efficacy.

Funding Source Level: Potential Impact (short and/or long term), Proposal Quality, Thematic Category

There always has been a general lack of funding for method development in itself

– method development is typically linked to clinical or biological questions in grant proposals.

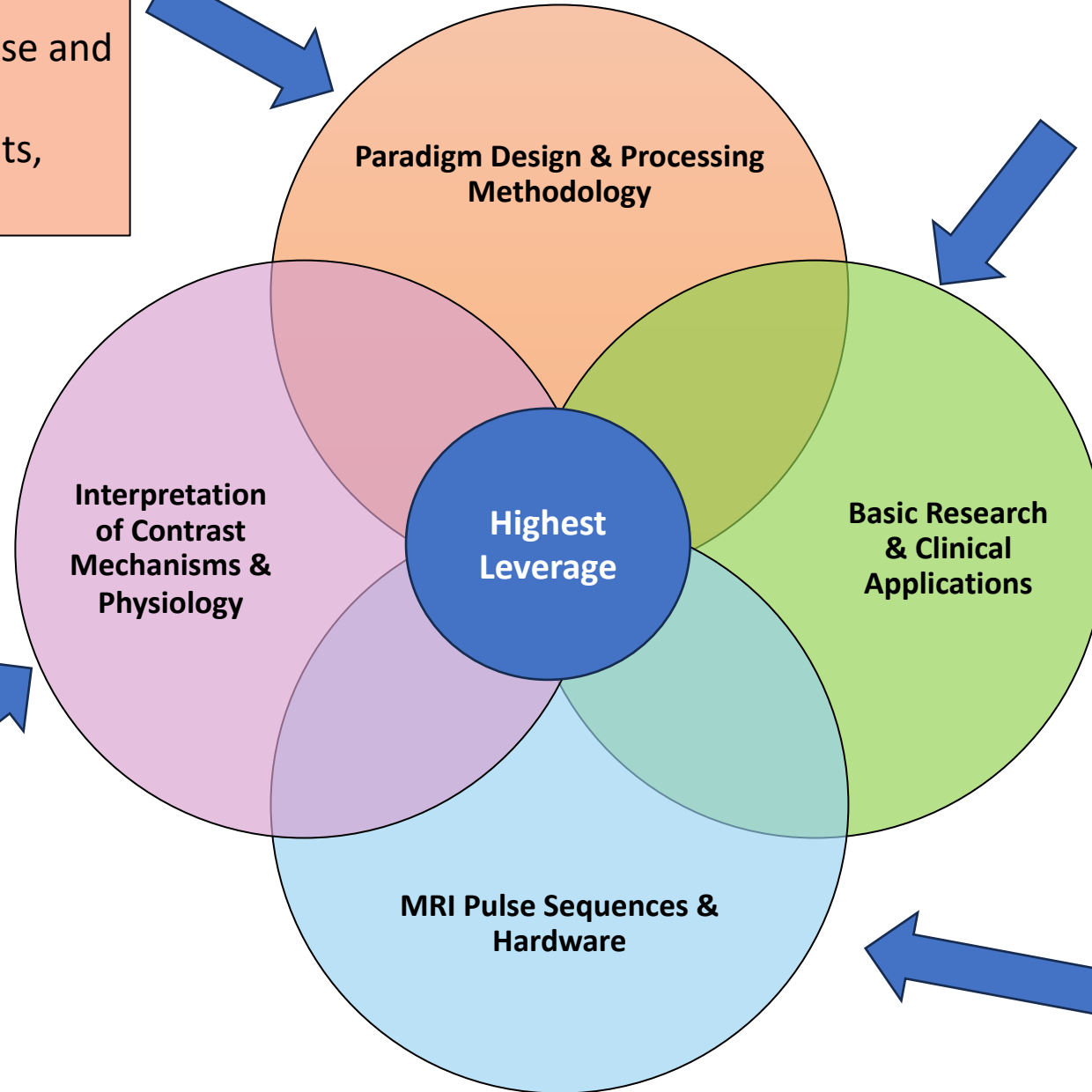
Natural Tension: Novelty & Impact vs Correctness



FMRI "Pillars"

- Capture neuronal activity, patterns, dynamics in time and space.
- Separate information from noise and artifact.
- Compare states, individual traits, and groups.

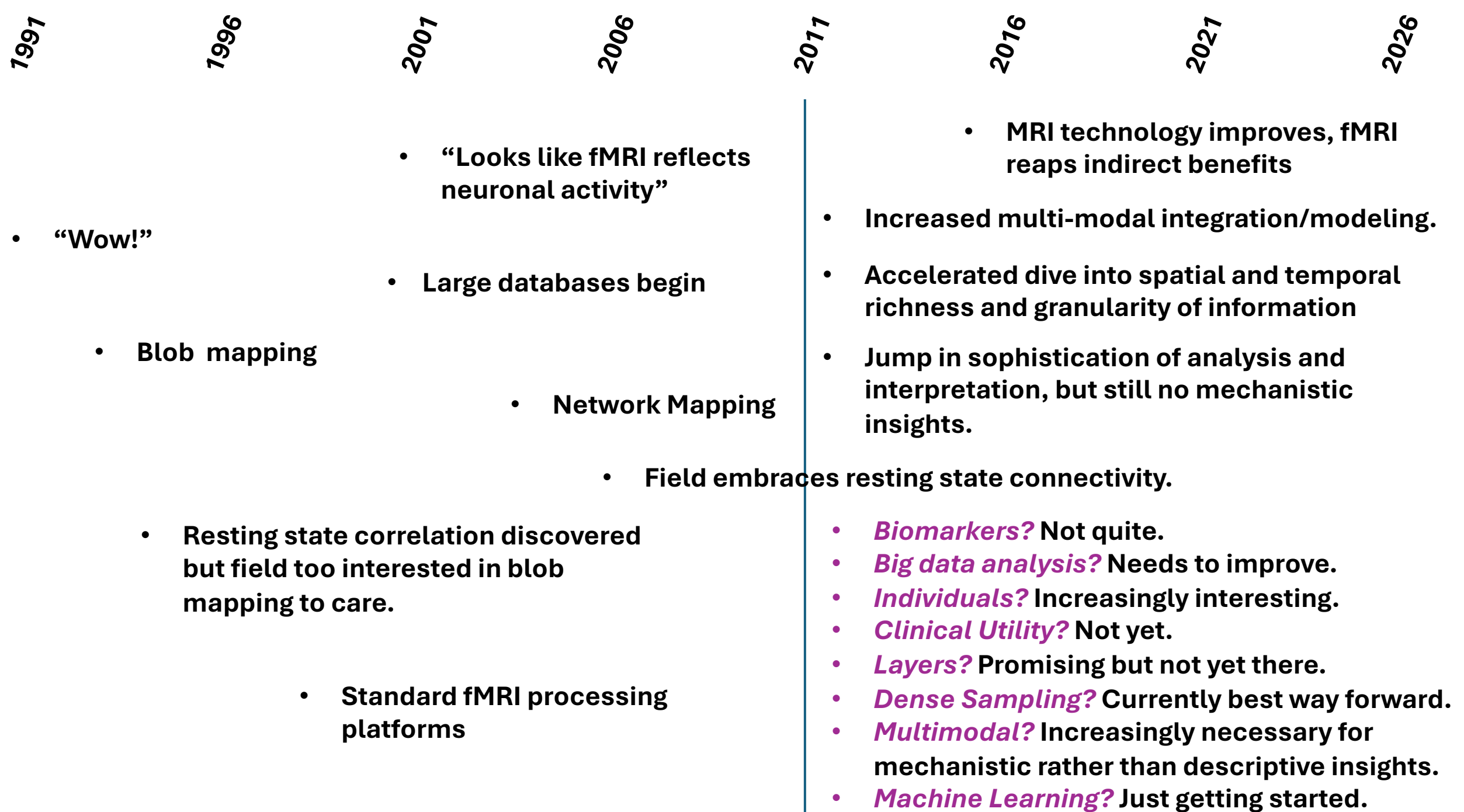
- Biomarker discovery and development
- Targets for neuromodulation
- Presurgical mapping
- Neurofeedback
- Uncover mechanisms and principles of functional brain organization.



- Speed
- Resolution
- Sensitivity
- Specificity
- Reproducibility
- Quantitation
- New Contrasts

- Identify relevant temporal and spatial structure.
- Multi-modal assessment: Relate signal to neuronal activity and non-neuronal measures.

1991	1996	2001	2006	2011	2016	2021	2026
Pulse Sequences and Hardware							
- First BOLD & ASL 1.5T & 4T 3T 4 channel receive coils	- EPI on most scanners - Multi-echo 8 channel receive coils	- SENSE, GRAPPA - Simultaneous EEG/fMRI - First Commercial 3T 7T - VASO 32 channel receive coils - Multi-echo available from vendors	SMS or Multi-band for fMRI	- VASO for layer fMRI 64 channel receive coils 3D EPI more widespread	- FDA clearance for 7T - Simultaneous EEG/fMRI @7T	- pTX - Local head gradient coil @7T “Next Gen”	
Interpretation, Contrast Mechanisms, and Physiology							
- Location confirmation - Resting state correlation - Biophysical Models - Parametric modulation - Echo time dependence - SE vs GE vs ASL comparisons	Mechanistic HRF models	- BOLD relates to LFP - Alpha/Beta negative correlation with BOLD	- Slow QPPs found - Gliovascular coupling	Calcium flux coupled to BOLD	Gamma positive correlation with BOLD		
Paradigms and Processing							
- Block designs - Event-related - Short/variable ISI Event-related “Topy” paradigms - AFNI	- Resting state correlation - Event-related cognition - Brain Voyager - Real-time fMRI	- FSL - MVPA - neurofeedback - fMRI Adaptation	- RSA - Intersubject Correlation - fMRI guided neuromodulation	- Generative Reconstruction - Human Connectome Project - Parcellation atlases - Open fMRI 1000 functional connectomes - Dynamic Resting State - Dense Sampling	- Brain Fingerprinting - Open neuro - UK Biobank (5K) - Covert neurofeedback	UK Biobank (100K)	



Some Significant Advances in fMRI over the years

Pulse sequences and Hardware

- *Multi-channel RF*
- *Multi-band acquisition (SENSE, GRAPPA) and Simultaneous Multislice (SMS)*
- *7T*
- *VASO*
- *Multi-echo*
- *3mm³ -> 0.5 mm³ resolution*

Interpretation

- *Electrophysiologic, Behavioral, Animal model (Ca²⁺, optogenetics, electrodes), confirmation.*
- *Tight behavioral confirmation (performance, attention, etc...).*
- *Individual and Population trait-level correlations.*

Paradigms and Processing

- *Resting state & Functional connectivity approaches*
- *Multivariate Decoding*
- *Phase-encoded stimuli (i.e. retinotopy), Fast event related, fMRI Adaptation, Naturalistic*
- *Dense or Deep sampling and Individual subject assessment*
- *Large Data Sets (i.e. HCP, UK Biobank)*
- *Standard processing platforms (i.e. AFNI, FSL...)*
- *Neurofeedback*
- *Standards and Reproducibility and Replicability Initiative (i.e. OpenNeuro)*

Applications

- *Whole brain maps correlated with behavior and state (research)*
- *Presurgical mapping, real-time feedback, longitudinal studies, Intervention measures (clinical)*

Common Criticisms

The signal is slow and coarse, variable over time and space, not fully understood, and not directly informative of neuronal mechanisms.

Mapping does not give insights into mechanisms and principles.

The images suffer from signal dropout and artifact and are sensitive to motion.

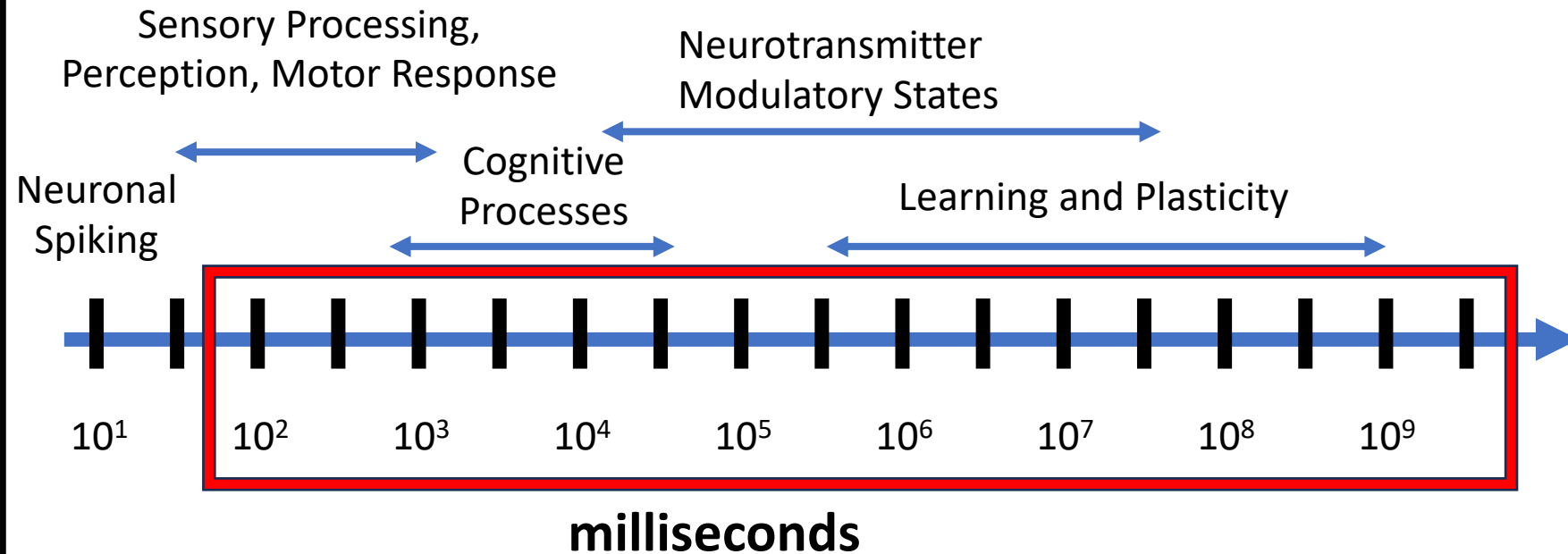
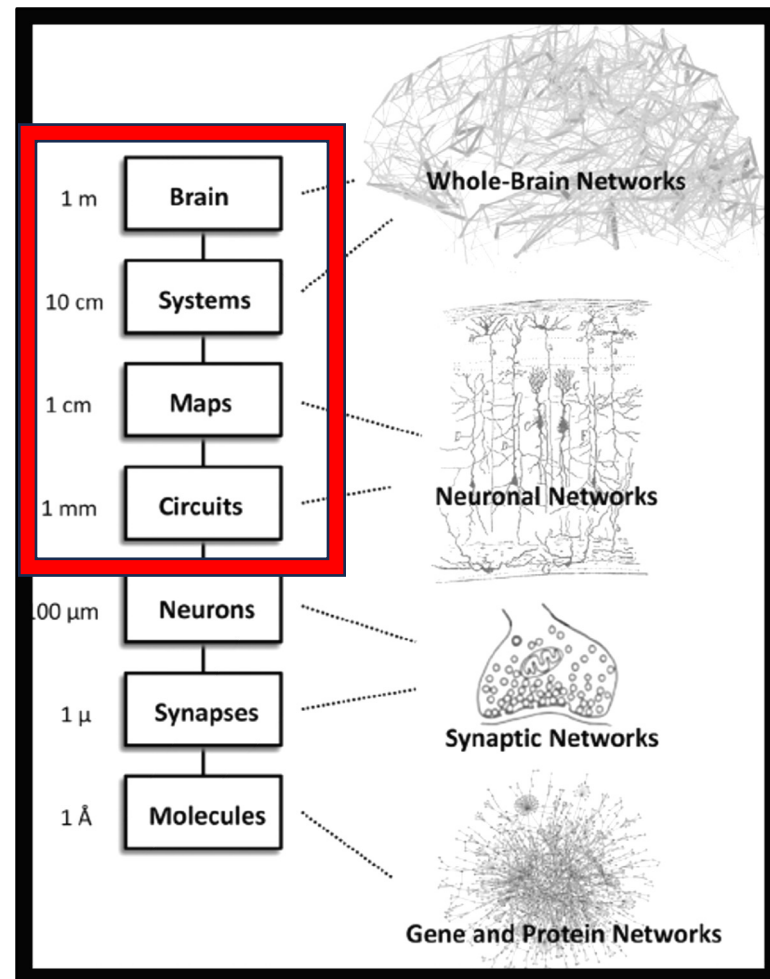
...but it's sensitive, robust, noninvasive, replicable if done well, and the best thing we have.

Most fMRI research has been towards understanding functional brain organization

The desire is that:

- *The signal means something (contains information)*
- *Is sensitive, precise, and repeatable.*
- *The spatial and temporal scales are relevant and useful.*

Spatial and Temporal Scales of Brain Function



Why do we want to improve it?

There is more information in the signal.

- Improvements in temporal/spatial resolution, interpretability, and processing methods provide leverage to develop *better models of noise and information*.
- fMRI doesn't suffer from a lack of sensitivity. We just haven't figured out how to fully wrangle the data from the backdrop of variability (in time, space, and across subjects).

Over 80,000 fMRI papers published...Impact of fMRI so far?

- fMRI **(dynamic) connectivity** has catalyzed new frameworks and directions in multimodal human brain research.
- fMRI has established a **brain network** perspective: relationships to tasks, behavior, states, and traits, and spontaneous engagement - and pathology...*but not yet sufficient providing mechanistic insights, nor for clinical utility.*
- fMRI has identified **changes** with learning, adaptation, and plasticity, and has helped to better understand processes such as attention, language, sensory integration, emotion, and cognition in general.
- fMRI has catalyzed rethinking of **Individual Differences & Similarities**, and **Categorization of Pathology** (RDoC, DSM-5).
- fMRI has catalyzed research in **Neurovascular coupling** and **brain energetics** as well as **CSF** and **vascular physiology**.

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Controversies							
- Brain or Vein? - Initial dip		- Post undershoot origin - White matter activation	- Dead Salmon - Voodoo correlations - Double dipping - Global signal regression - Diffusion changes w/activation.	- Replication Crisis - Retraction due to systematic motion	- Cluster failure - Many analysis different results (NARPS)	- BWAS & >1000 subjects needed - DIANA paper controversy	

Controversies

Practices that may be incorrect, misleading, or discarding information:

- *Use of global signal regression.*
- *Interpretation of “Connectivity.”*
- *Thresholding.*
- *Simple regressor models.*
- *Assumptions of about subject homogeneity.*
- *Static connectivity measures.*

Non-reproduced findings:

- *Activation-induced changes in:
diffusion, neuronal currents, etc..*
- *Activation-induced BOLD in white matter*
- *Pre-undershoot*
- *Many small N group comparisons*

Shortcomings/Curiosities Amplified by Non-experts in media:

- *Dead Salmon (multiple comparisons -> false positives)*
- *Double dipping (voodoo correlations)*
- *Clustering Conundrum*
- *Multi-center single data set analysis and findings all over the place.*
- *1000's of subjects (Big Data BWAS Problem)*
- *Hemodynamic activation but no electrophysiology signatures.*
- *Ratio of flow/BOLD/CMRO₂ different in different regions and for activation vs. deactivation.*

The Dead Salmon Controversy

Ig Nobel Prize 2012

REFERENCE: “[Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: An argument for multiple comparisons correction](#),” Craig M. Bennett, Abigail A. Baird, Michael B. Miller, and George L. Wolford, poster, 15th Annual Meeting of the Organization for Human Brain Mapping, San Francisco, CA, June 2009.

REFERENCE: “[Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Multiple Comparisons Correction](#),” Craig M. Bennett, Abigail A. Baird, Michael B. Miller, and George L. Wolford, *Journal of Serendipitous and Unexpected Results*, vol. 1, no. 1, 2010, pp. 1-5.

ATTENDING THE CEREMONY: Craig Bennett, Abigail Baird, Michael Miller, and George Wolford

Need to adjust for multiple comparisons producing false positives.



Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: An argument for multiple comparisons correction

Craig M. Bennett¹, Abigail A. Baird², Michael B. Miller¹, and George L. Wolford³

¹ Psychology Department, University of California Santa Barbara, Santa Barbara, CA; ² Department of Psychology, Vassar College, Poughkeepsie, NY;

³ Department of Psychological & Brain Sciences, Dartmouth College, Hanover, NH

INTRODUCTION

With the extreme dimensionality of functional neuroimaging data comes extreme risk for false positives. Across the 130,000 voxels in a typical fMRI volume the probability of a false positive is almost certain. Correction for multiple comparisons should be completed with these datasets, but is often ignored by investigators. To illustrate the magnitude of the problem we carried out a real experiment that demonstrates the danger of not correcting for chance properly.

METHODS

Subject. One mature Atlantic Salmon (*Salmo salar*) participated in the fMRI study. The salmon was approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning.

Task. The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence. The salmon was asked to determine what emotion the individual in the photo must have been experiencing.

Design. Stimuli were presented in a block design with each photo presented for 10 seconds followed by 12 seconds of rest. A total of 15 photos were displayed. Total scan time was 5.5 minutes.

Preprocessing. Image processing was completed using SPM2. Preprocessing steps for the functional imaging data included a 6-parameter rigid-body affine realignment of the fMRI timeseries, coregistration of the data to a T₁-weighted anatomical image, and 8 mm full-width at half-maximum (FWHM) Gaussian smoothing.

Analysis. Voxelwise statistics on the salmon data were calculated through an ordinary least-squares estimation of the general linear model (GLM). Predictors of the hemodynamic response were modeled by a boxcar function convolved with a canonical hemodynamic response. A temporal high pass filter of 128 seconds was included to account for low frequency drift. No autocorrelation correction was applied.

Voxel Selection. Two methods were used for the correction of multiple comparisons in the fMRI results. The first method controlled the overall false discovery rate (FDR) and was based on a method defined by Benjamini and Hochberg (1995). The second method controlled the overall familywise error rate (FWER) through the use of Gaussian random field theory. This was done using algorithms originally devised by Friston et al. (1994).

DISCUSSION

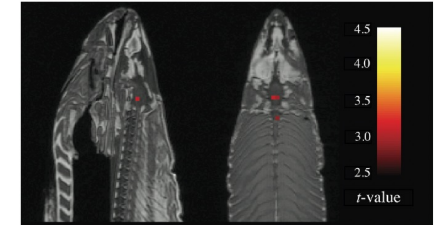
Can we conclude from this data that the salmon is engaging in the perspective-taking task? Certainly not. What we can determine is that random noise in the EPI timeseries may yield spurious results if multiple comparisons are not controlled for. Adaptive methods for controlling the FDR and FWER are excellent options and are widely available in all major fMRI analysis packages. We argue that relying on standard statistical thresholds ($p < 0.001$) and low minimum cluster sizes ($k > 8$) is an ineffective control for multiple comparisons. We further argue that the vast majority of fMRI studies should be utilizing multiple comparisons correction as standard practice in the computation of their statistics.

REFERENCES

Benjamini Y and Hochberg Y (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B*, 57:289-300.

Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, and Evans AC. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping*, 1:214-220.

GLM RESULTS

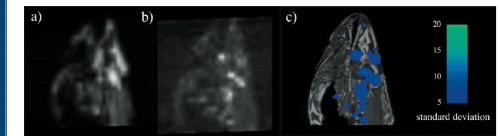


A t -contrast was used to test for regions with significant BOLD signal change during the photo condition compared to rest. The parameters for this comparison were $t(131) > 3.15$, $p(\text{uncorrected}) < 0.001$, 3 voxel extent threshold.

Several active voxels were discovered in a cluster located within the salmon's brain cavity (Figure 1, see above). The size of this cluster was 81 mm³ with a cluster-level significance of $p = 0.001$. Due to the coarse resolution of the echo-planar image acquisition and the relatively small size of the salmon brain further discrimination between brain regions could not be completed. Out of a search volume of 8064 voxels a total of 16 voxels were significant.

Identical t -contrasts controlling the false discovery rate (FDR) and familywise error rate (FWER) were completed. These contrasts indicated no active voxels, even at relaxed statistical thresholds ($p = 0.25$).

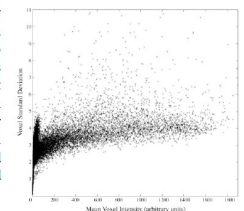
VOXELWISE VARIABILITY



To examine the spatial configuration of false positives we completed a variability analysis of the fMRI timeseries. On a voxel-by-voxel basis we calculated the standard deviation of signal values across all 140 volumes.

We observed clustering of highly variable voxels into groups near areas of high voxel signal intensity. Figure 2a shows the mean EPI image for all 140 image volumes. Figure 2b shows the standard deviation values of each voxel. Figure 2c shows thresholded standard deviation values overlaid onto a high-resolution T₁-weighted image.

To investigate this effect in greater detail we conducted a Pearson correlation to examine the relationship between the signal in a voxel and its variability. There was a significant positive correlation between the mean voxel value and its variability over time ($r = 0.54$, $p < 0.001$). A scatterplot of mean voxel signal intensity against voxel standard deviation is presented to the right.



Circular Analysis and Double Dipping

Circular analysis in systems neuroscience – the dangers of double dipping

Nikolaus Kriegeskorte, W Kyle Simmons, Patrick SF Bellgowan, and Chris I Baker Laboratory of Brain and Cognition, National Institute of Mental Health

Nat Neurosci. 2009 May ; 12(5): 535–540. doi:10.1038/nn.2303.

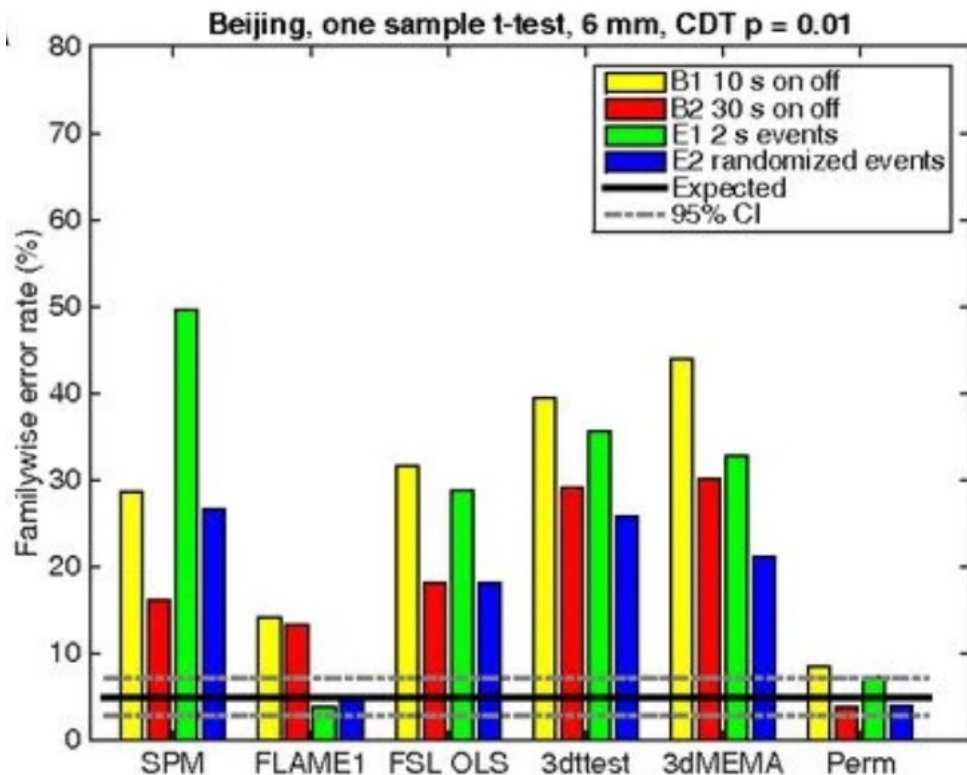
Using the same dataset for both **selection and **analysis** leads to distorted statistics and invalid conclusions.**



The Clustering Conundrum

Eklund, A.; Nichols, T. E.; Knutsson, H. Cluster Failure: Why fMRI Inferences for Spatial Extent Have Inflated False-Positive Rates. *Proceedings of the National Academy of Sciences* **2016**, 113 (28), 7900–7905. <https://doi.org/10.1073/pnas.1602413113>.

“Our results suggest that the principal cause of the invalid cluster inferences is spatial autocorrelation functions that do not follow the assumed Gaussian shape.”



Impacted a huge fraction of papers...putting all of fMRI into doubt.

Did it *really* change any conclusions of any papers?

...Likely Not

Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity

[Yevgeniy B. Sirotnin](#) & [Aniruddha Das](#) 

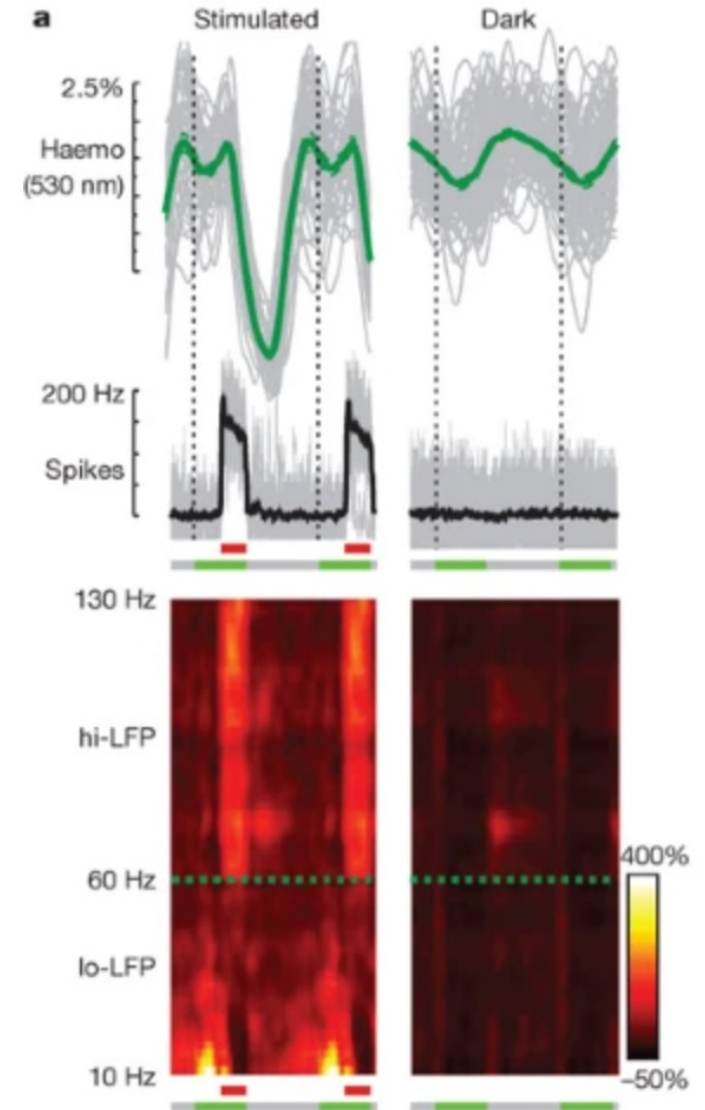
[Nature](#) **457**, 475–479 (2009) | [Cite this article](#)

5694 Accesses | **311** Citations | **45** Altmetric | [Metrics](#)

“anticipatory” HRF that’s purely vascular.

Likely: differences in sensitivity & overlapping HRF

Handwerker, D. A.; Bandettini, P. A. Simple Explanations before Complex Theories: Alternative Interpretations of Sirotnin and Das’ Observations. Neuroimage **2011**, 55 (4), 1419–1422

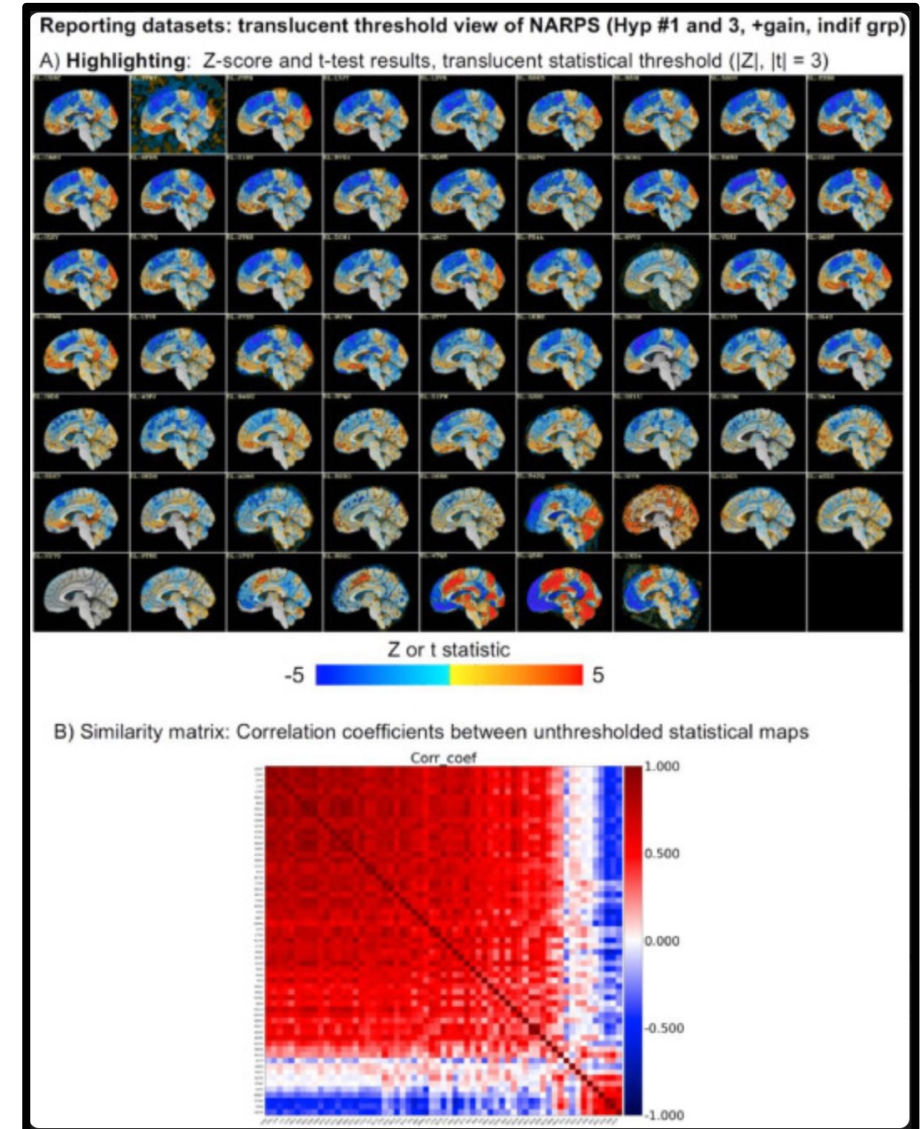


The Single Data Set, Many Analyses

Variability in the analysis of a single neuroimaging dataset by many teams

Botvinik-Nezer, R., Holzmeister, F., Camerer, C. F., et al.
(2020). *Nature*, 582(7810), 84-88. DOI: [10.1038/s41586-020-2314-9](https://doi.org/10.1038/s41586-020-2314-9).

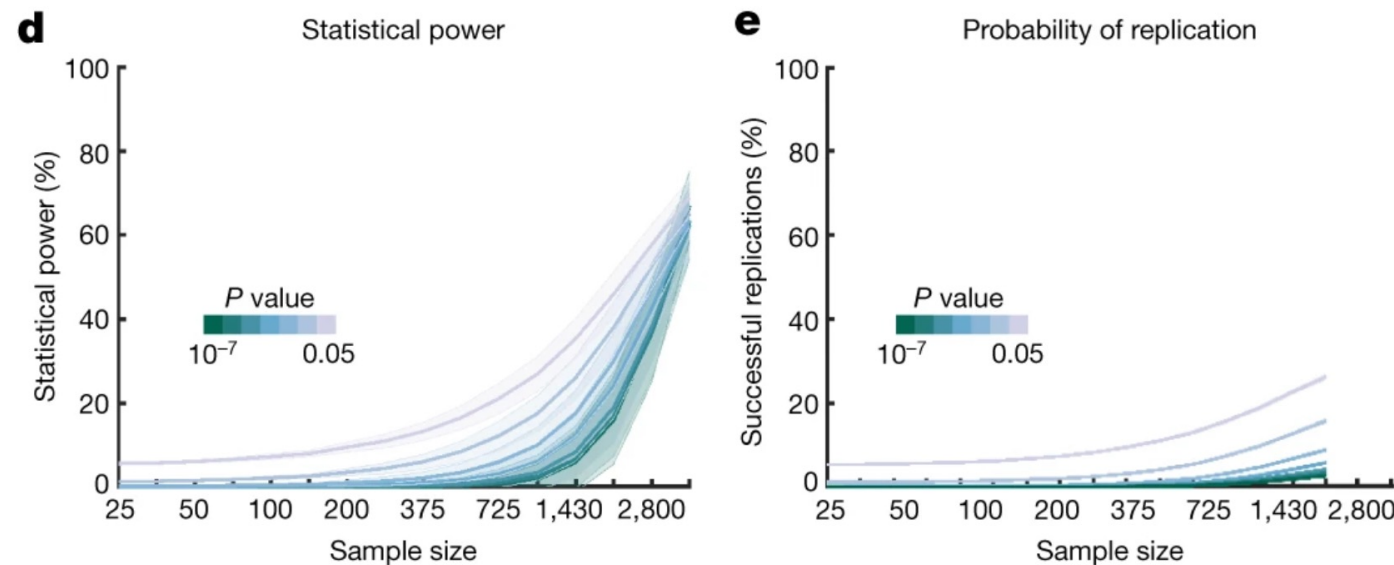
- 70 teams analyzed the same data set.
- Gambling task
- Testing 9 pre-defined hypotheses
- Results differed in proportion to threshold level
- Binary hypotheses decisions further stratified results
- Unthresholded results are highly correlated.
- Smoothness increased agreement.
- Model functions differed?



1000's of subjects to see a reproducible difference?

Reproducible Brain-Wide Association Studies Require Thousands of Individuals.

Marek, S.; Tervo-Clemmens, B.; Calabro, F. J.; Montez, D. F.; Kay, B. P.; Hatoum, ...Luna, B.; Fair, D. A.; Dosenbach, N. U. F. *Nature* **2022**, 603 (7902), 654–660.
<https://doi.org/10.1038/s41586-022-04492-9>.



Issues?

Population heterogeneity
Individual Parcellation variation
NOT a problem of fMRI sensitivity

Methodological variability Botvinik-Nezer, R. et al. Variability in the analysis of a single neuroimaging dataset by many teams. *Nature* **582**, 84–88 (2020).

Data mining Nuzzo, R. Scientific method: Statistical errors. *Nature* **506**, 150–152 (2014).

Overfitting Hawkins, D. M. The problem of overfitting. *J. Chem. Inf. Comput. Sci.* **44**, 1–12 (2004).

Confirmation and publication bias Bishop, D. How scientists can stop fooling themselves over statistics. *Nature* **584**, 9 (2020).

Inadequate Statistical Power Button, K. S. et al. Power failure: why small sample size undermines the reliability of neuroscience. *Nat. Rev. Neurosci.* **14**, 365–376 (2013).

Mysteries

- Why does the BOLD response happen? (activation -> blood hyperoxygenation)
- What are the neuronal/hemodynamic mechanisms behind BOLD transients, nonlinearities, inhomogeneities?
- Is inhibition vs excitation differentiable?
- What are the sources and types of spontaneous fluctuations and connectivity? What is the global signal?
- What is the “purpose” of resting state fMRI?
- What are we missing in activation? Simple regressors, low sensitivity, large/fixed parcellations...
- Why is the parcellation size what it is? Are there finer natural parcellations? What is meaningful?
- Do parcellations vary across individuals and time?
- Best way to compare brains across/within groups and across individuals at different resolutions?
- How relevant is the spatial/temporal scale of MRI for deriving principles of cognition?

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Why does BOLD response (activation -> blood hyperoxygenation) happen?

Revisiting what I thought was a settled question..

Received: 5 October 2022 | Revised: 22 April 2023 | Accepted: 2 May 2023

DOI: 10.1111/jnc.15839

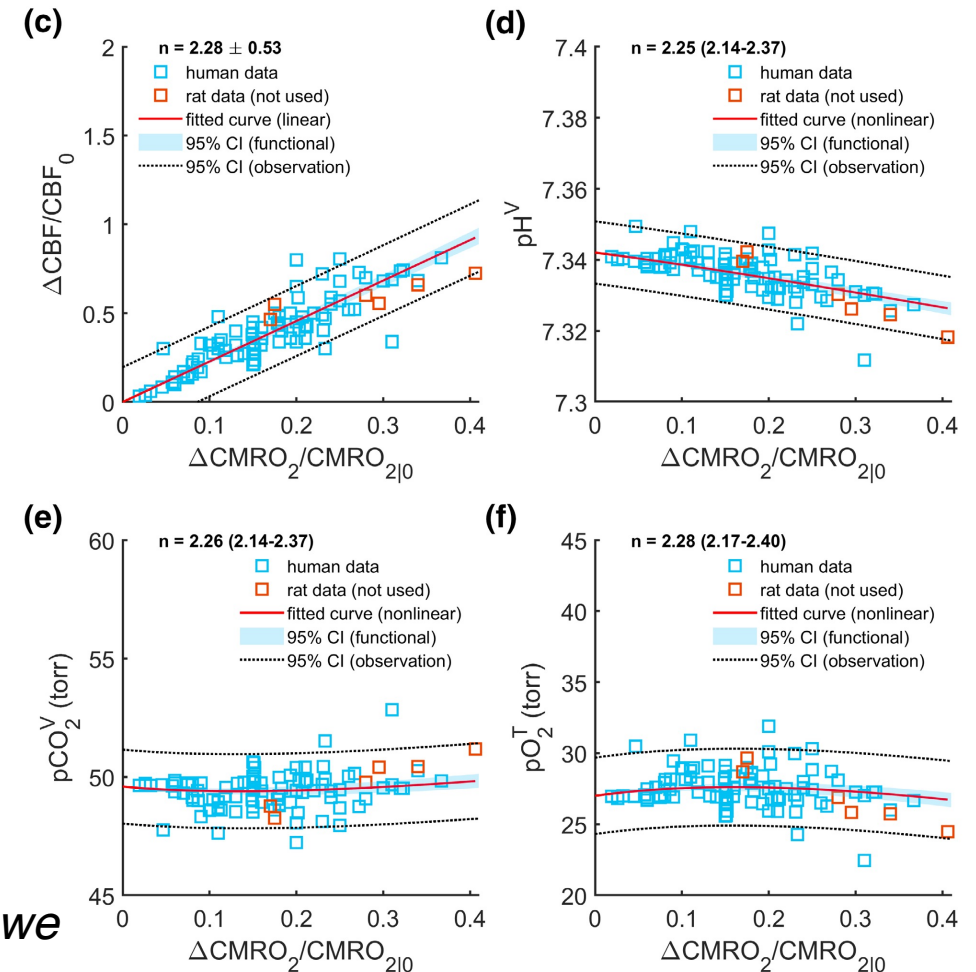
ORIGINAL ARTICLE



Neurovascular coupling is optimized to compensate for the increase in proton production from nonoxidative glycolysis and glycogenolysis during brain activation and maintain homeostasis of pH, $p\text{CO}_2$, and $p\text{O}_2$

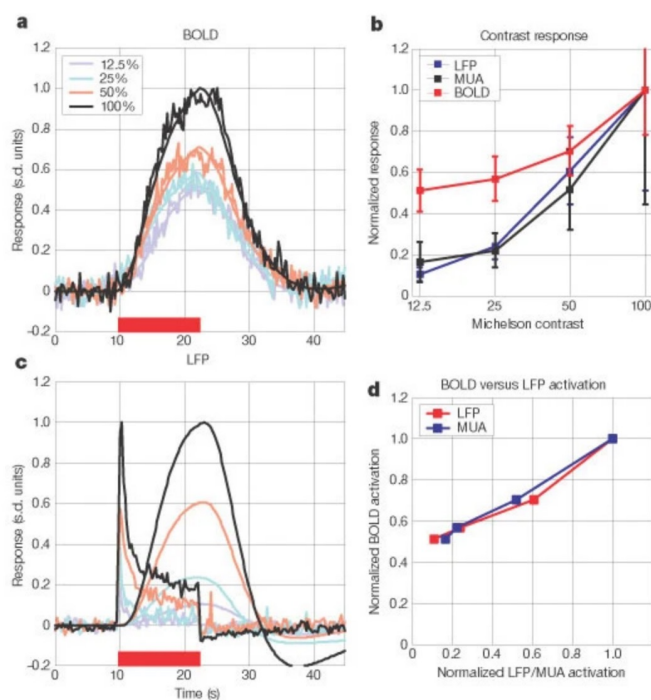
Mauro DiNuzzo¹ | Gerald A. Dienel^{2,3} | Kevin L. Behar⁴ | Ognjen A. Petroff⁵ |
Helene Benveniste^{6,7} | Fahmeed Hyder^{7,8} | Federico Giove^{1,9} |
Shalom Michaeli¹⁰ | Silvia Mangia¹⁰ | Suzana Herculano-Houzel^{11,12,13} |
Douglas L. Rothman^{7,8}

“Explanations for the high CBF versus CMRO₂ slope, termed neurovascular coupling (NVC) constant, focused on maintenance of tissue oxygenation to support mitochondrial ATP production”... Here, we hypothesize that the NVC constant and the capillary oxygen mass transfer coefficient (which in combination determine OEF) are co-regulated during activation to maintain simultaneous homeostasis of pH and partial pressure of CO₂ and O₂.”



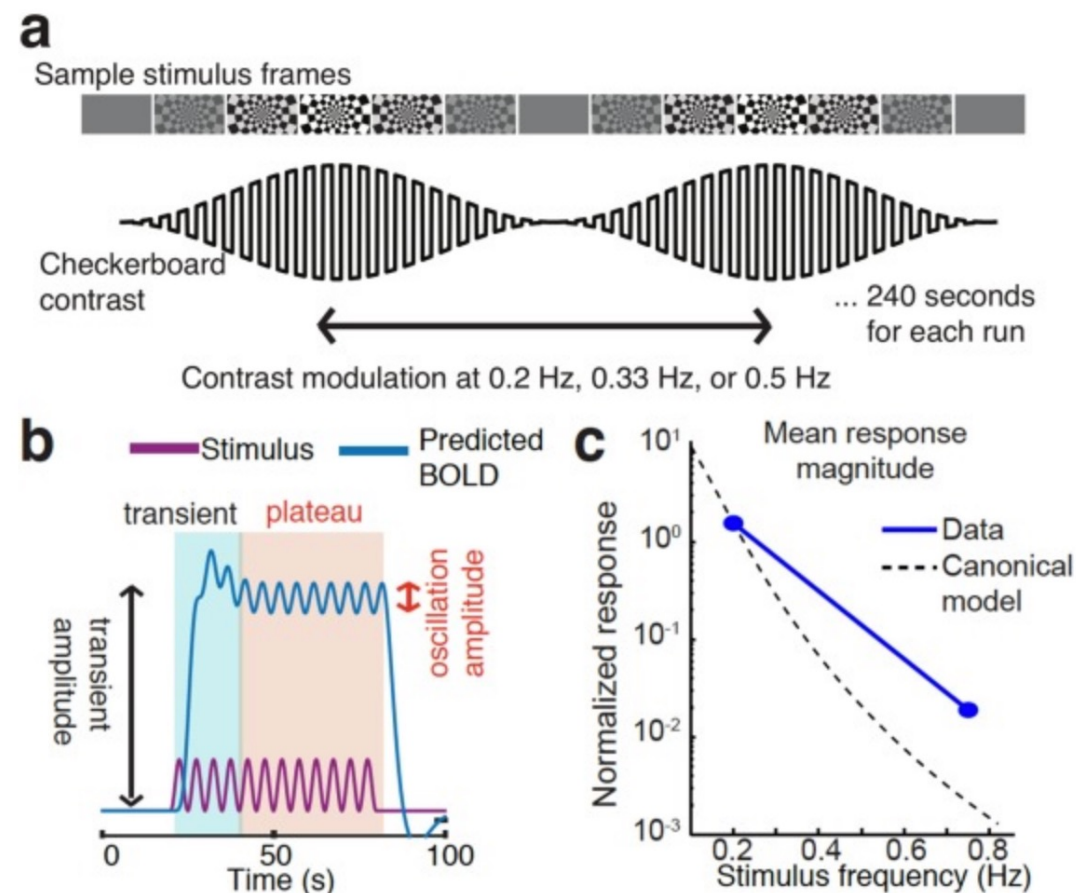
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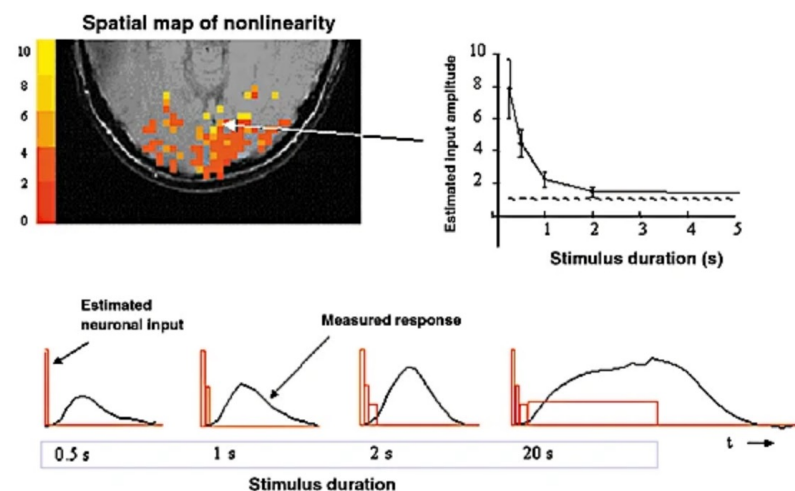


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Nonlinearities



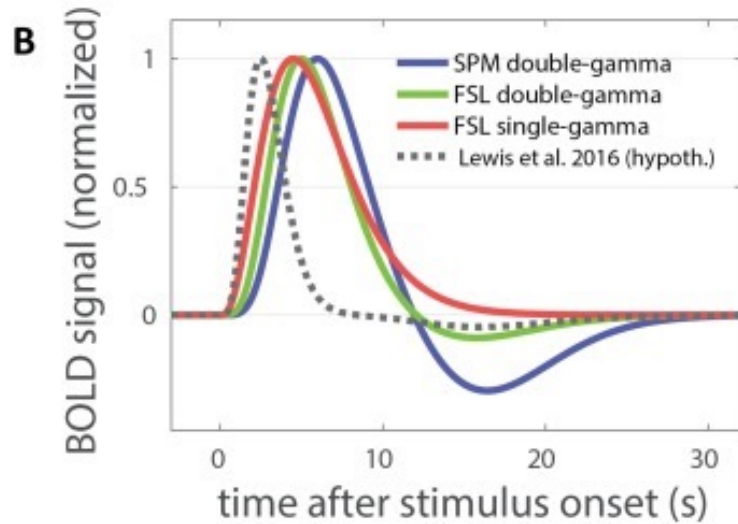
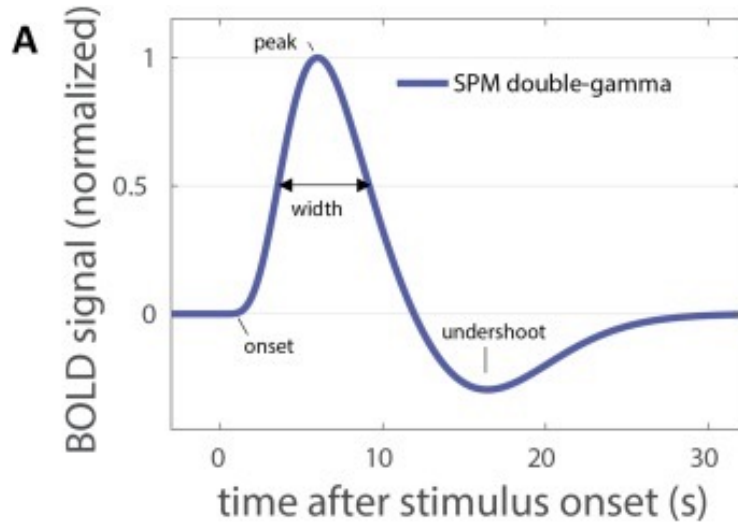
Logothetis et al, Nature 412, 150-157 (2001)



Polimeni and Lewis, Progress in Neurobiology, (2021)

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

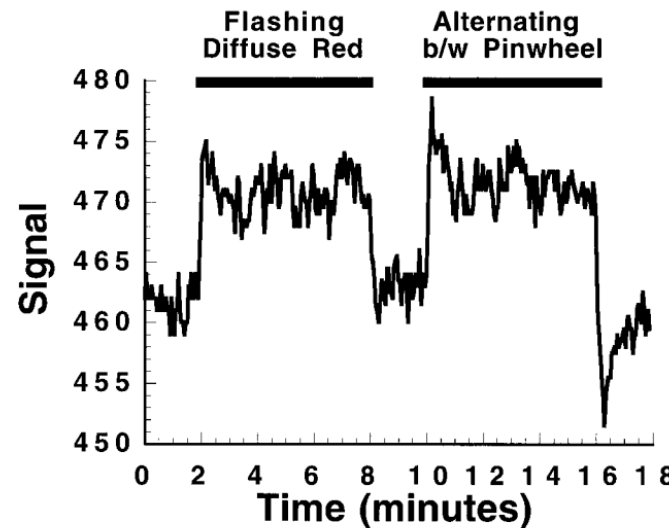
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Task timing

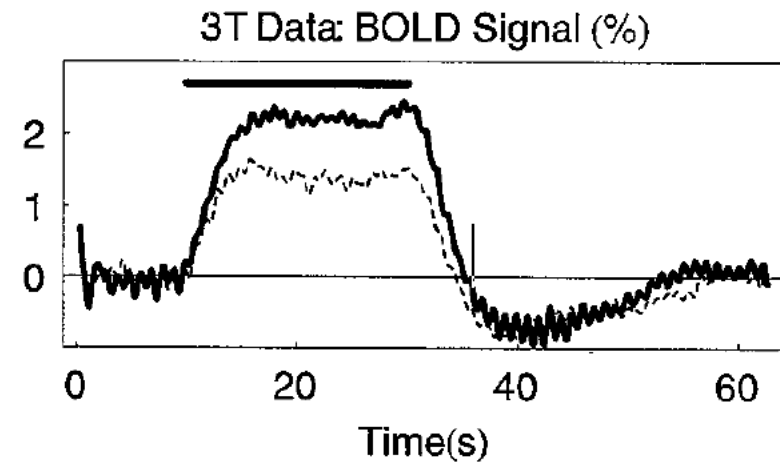
Depends on location, task, timing, and pulse sequence

Post undershoot



Stimulus

Bandettini et al, HBM (1997)



Diffusion weighting

Buxton et al, ISMRM (1996)

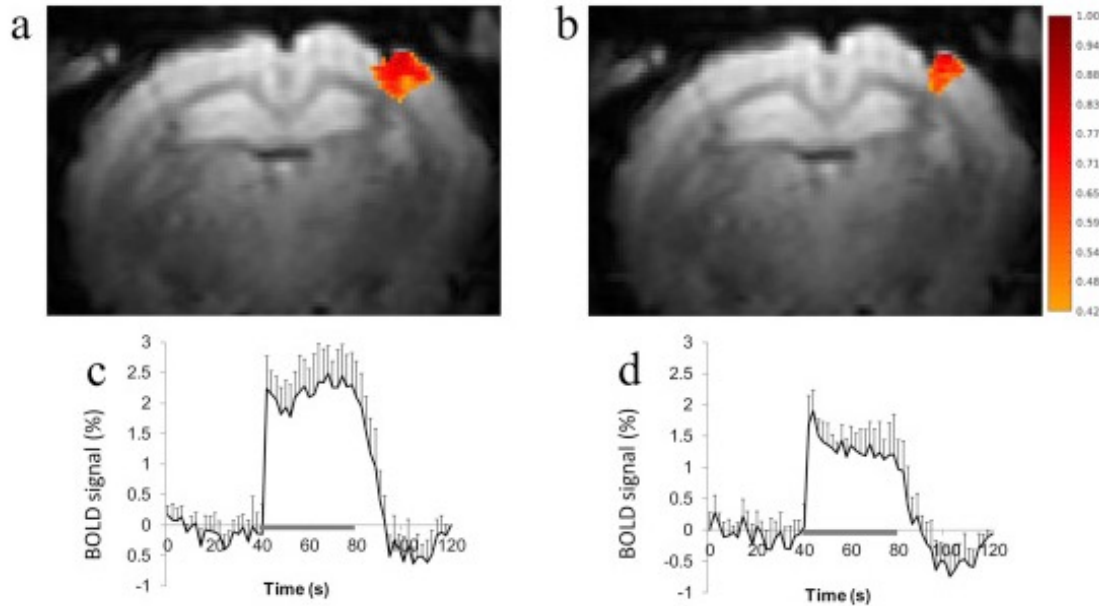
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- Is inhibition vs excitation differentiable?

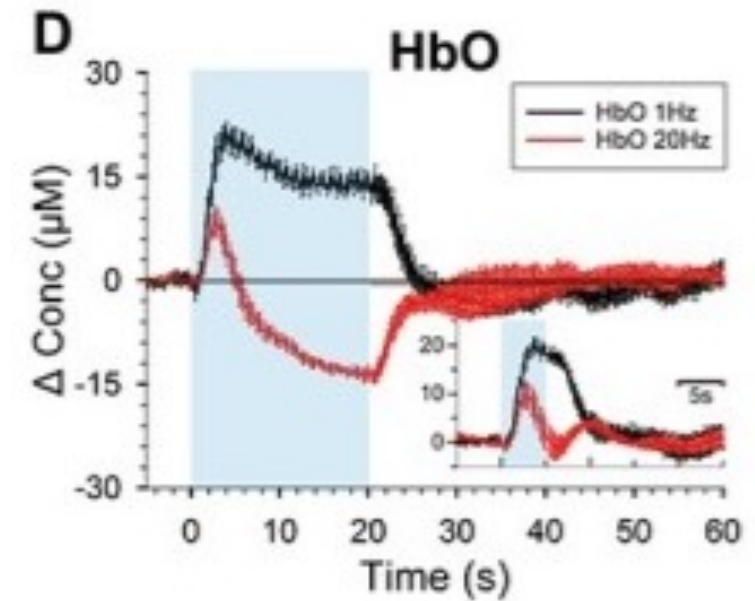
Inhibition vs. excitation effects on BOLD?

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



DP Aksenov et al, NeuroImage (2019)

Optogenetic stim: Excitatory and **Inhibitory** Neurons



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

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- Why is the parcellation size what it is? Are there finer natural parcellations? What is meaningful?
- Do parcellations vary across individuals and time?
- Best way to compare brains across/within groups and across individuals at different resolutions?
- How relevant is the spatial/temporal scale of MRI for deriving principles of cognition?

What contributes to spontaneous fluctuations?

Spontaneous Neuronal Activity

- conscious thought
- unconscious processes
- arousal, vigilance

Vasomotion

Respiration

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

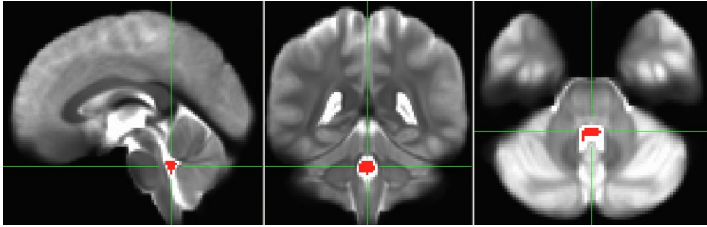
Cardiac Pulsation

Thermal Noise

Motion

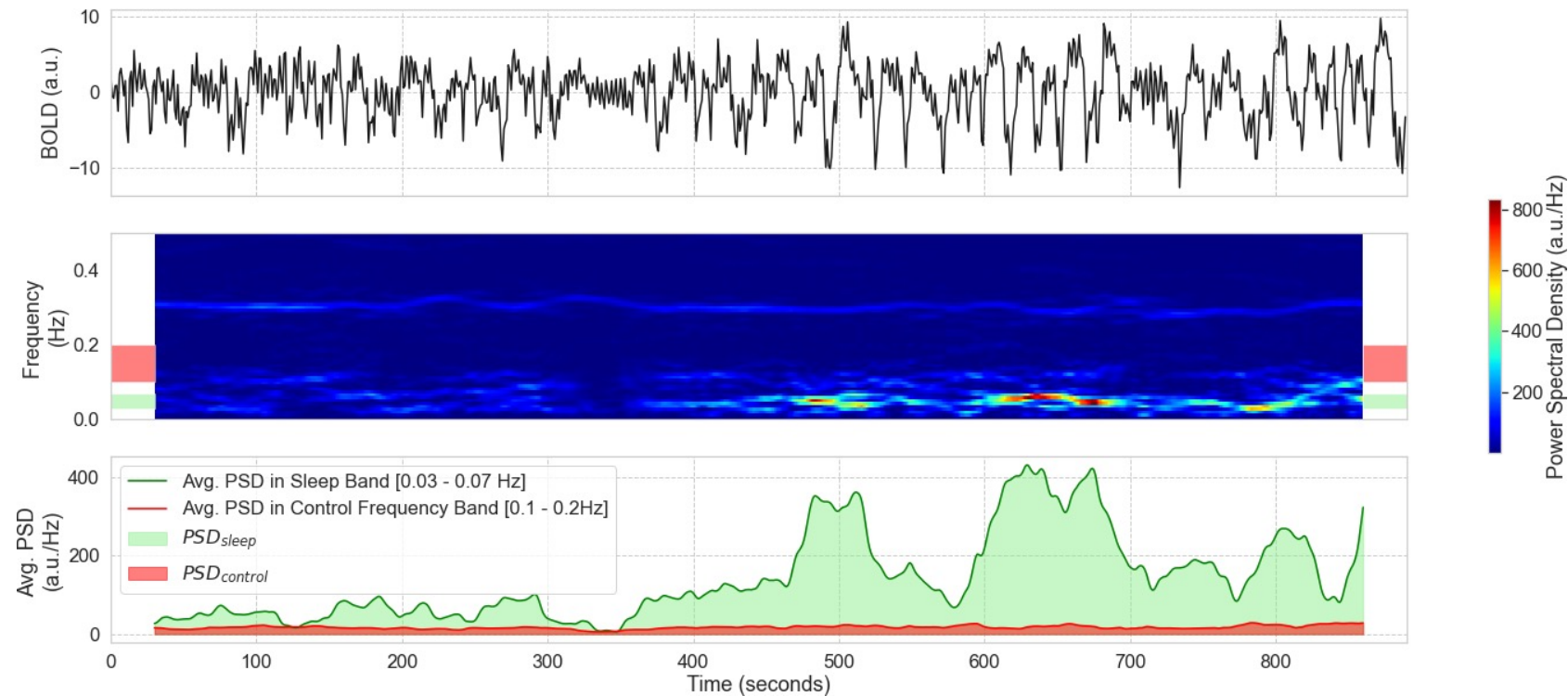
Scanner Instability

Slow fluctuations with reduced arousal and sleep



Global changes with arousal

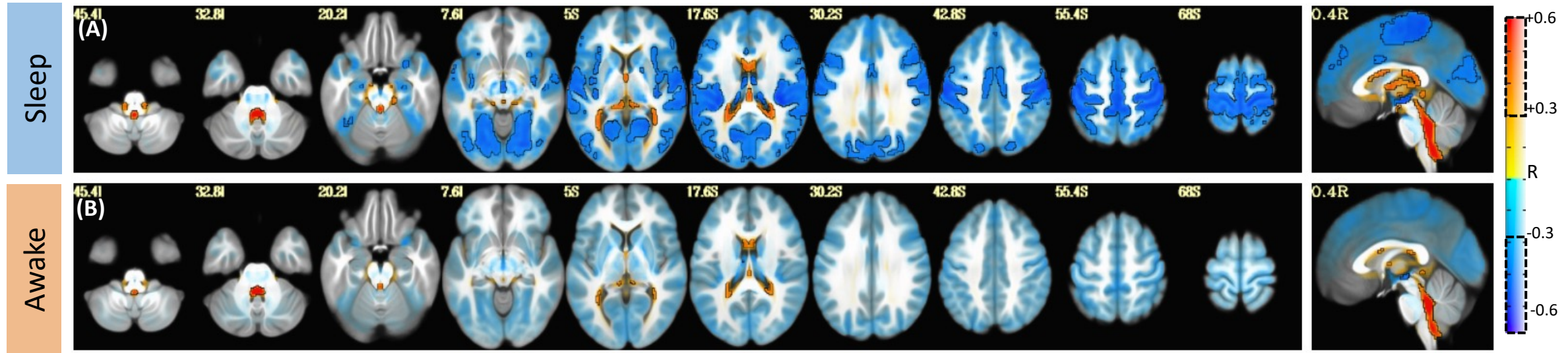
Power around 0.05 Hz in 4th Ventricle



J. Gonzalez-Castillo, I. Fernandez, D.A. Handwerker, P.A. Bandettini, Ultra-slow fMRI fluctuations in the fourth ventricle as a marker of drowsiness, *NeuroImage* [259](#), 119424 (2022)

Global changes with Arousal

(Cortex out of phase with 4th ventricle).....CSF, BOLD?

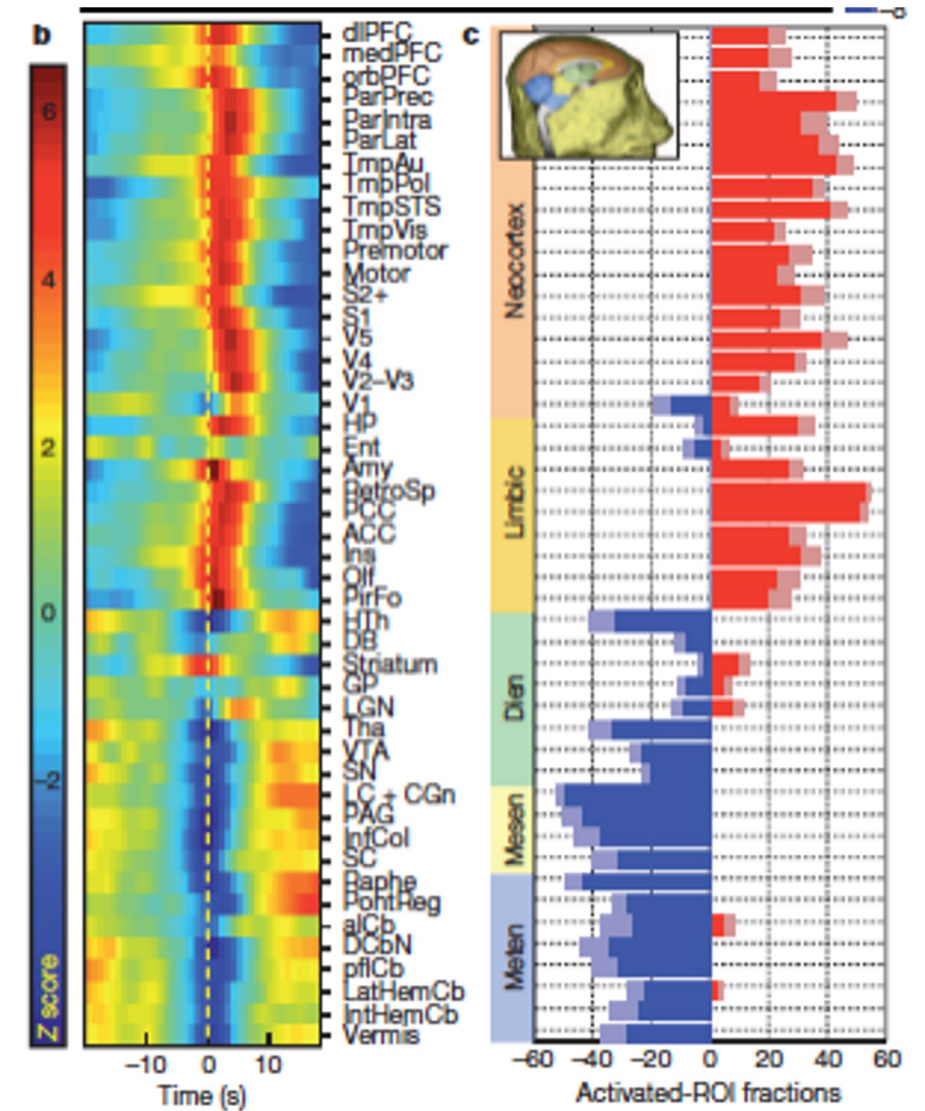
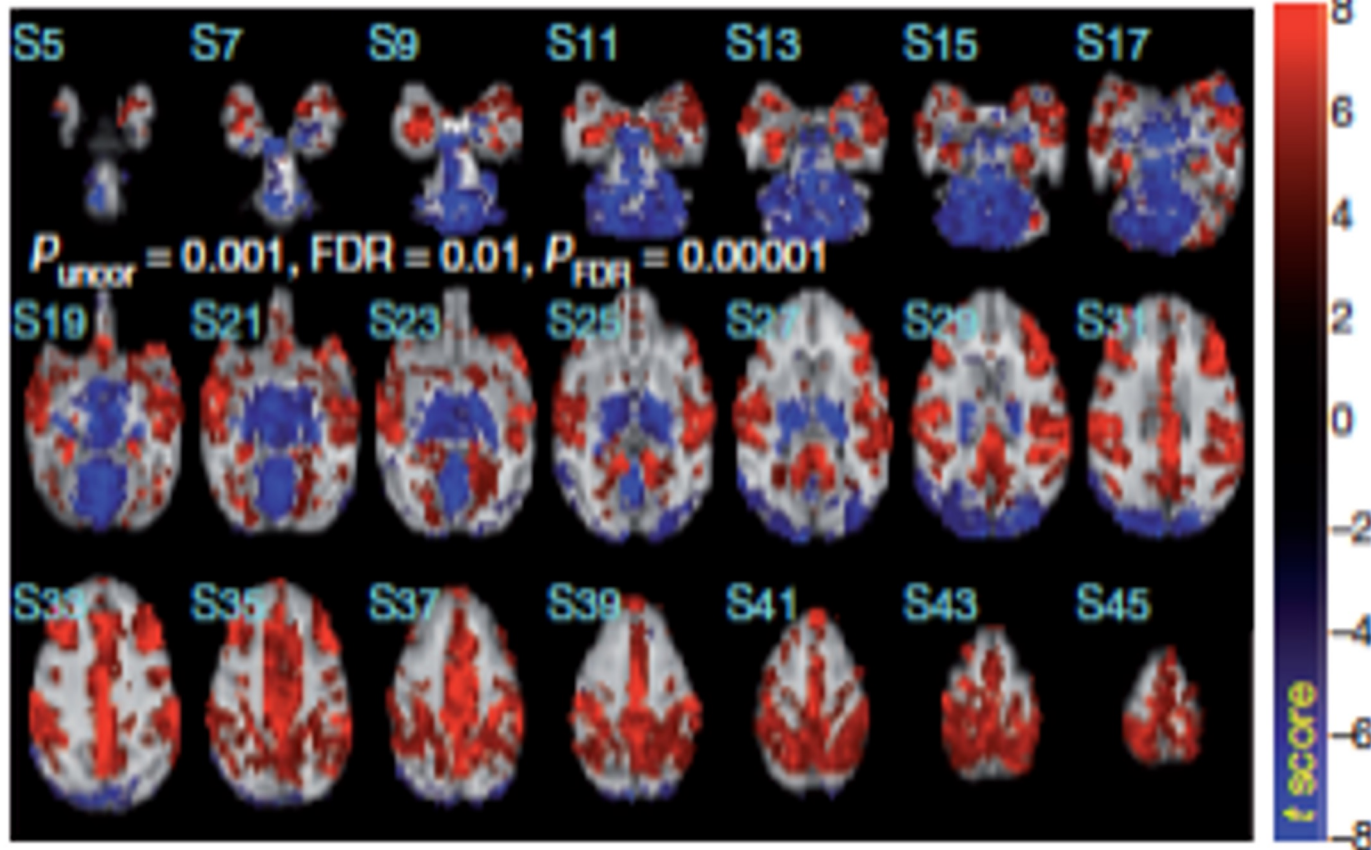


J. Gonzalez-Castillo, I. Fernandez, D.A. Handwerker, P.A. Bandettini, Ultra-slow fMRI fluctuations in the fourth ventricle as a marker of drowsiness, NeuroImage [259](#), 119424 (2022)

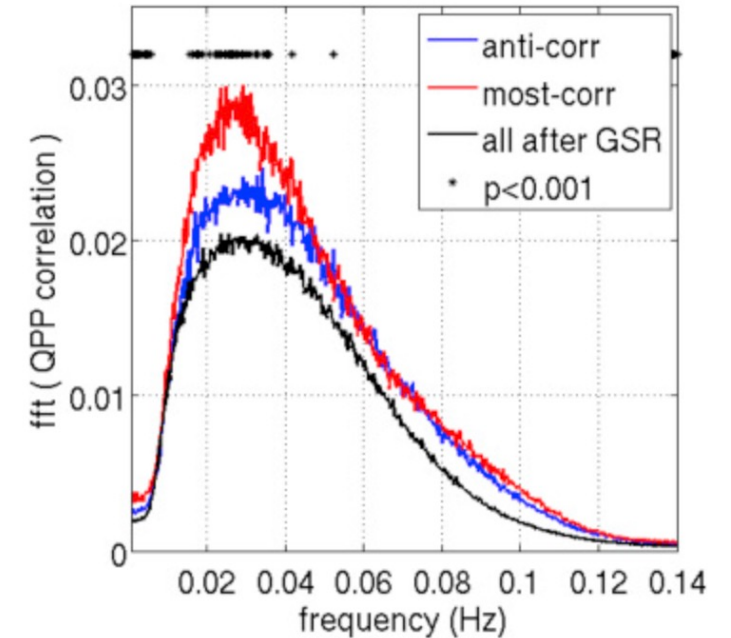
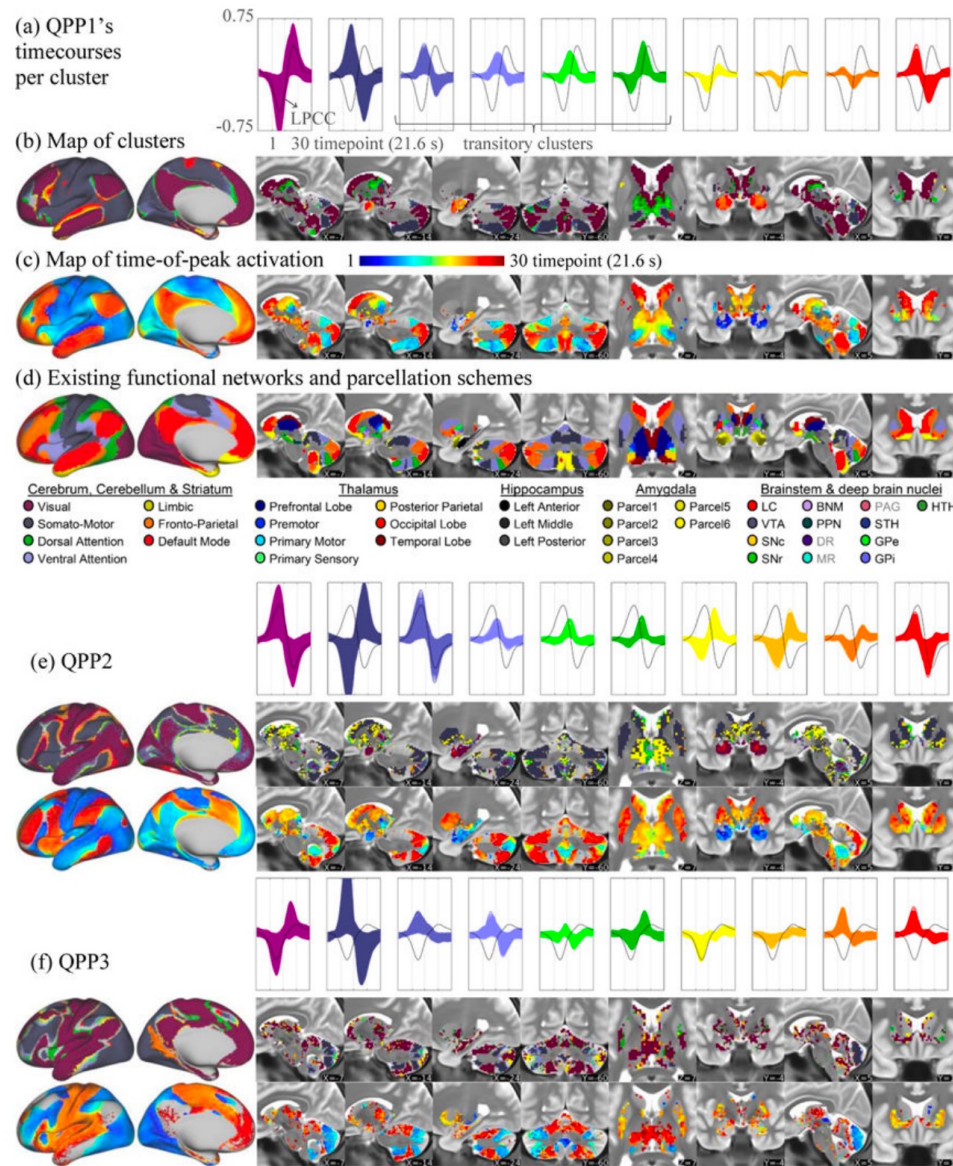
Anti-correlation of subcortical with cortical drowsiness/sleep related fluctuations

Hippocampal Ripple Induced Anticorrelated Activity

a



Quasi-Periodic Patterns



Yousefi, B.; Keilholz, S. Propagating Patterns of Intrinsic Activity along Macroscale Gradients Coordinate Functional Connections across the Whole Brain. *NeuroImage* **2021**, *231*, 117827.

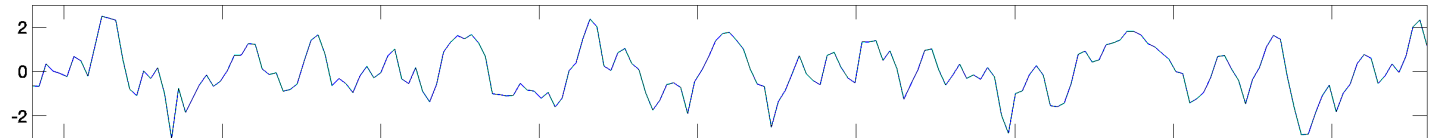
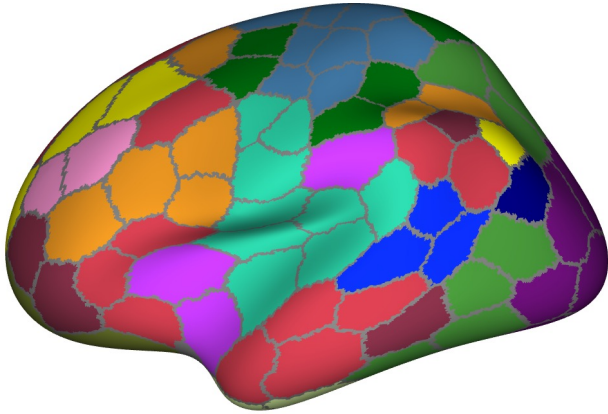
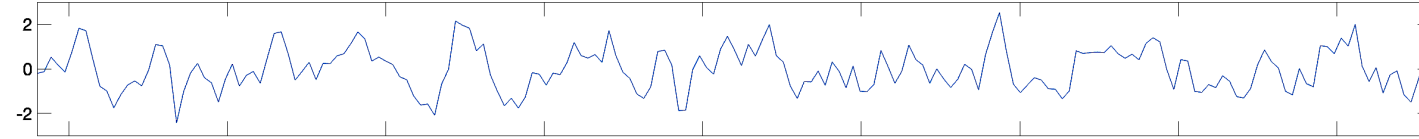
<https://doi.org/10.1016/j.neuroimage.2021.117827>.

Addressing Resting State with Edge Analysis

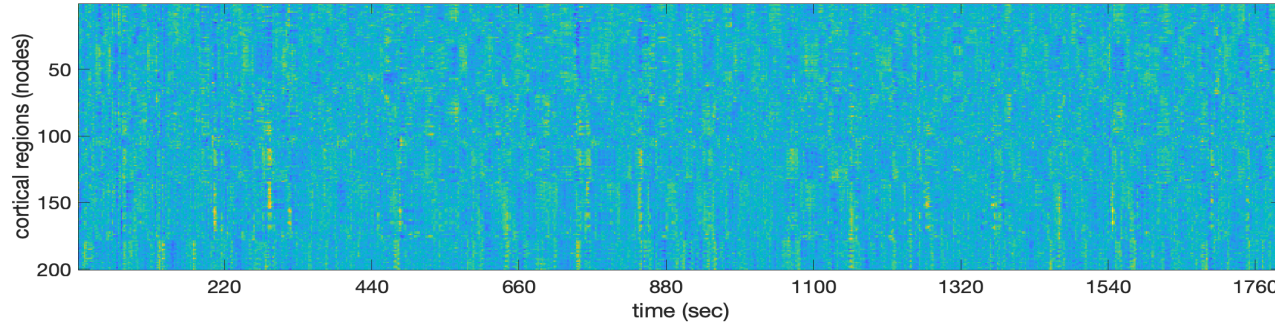


Josh Faskowitz

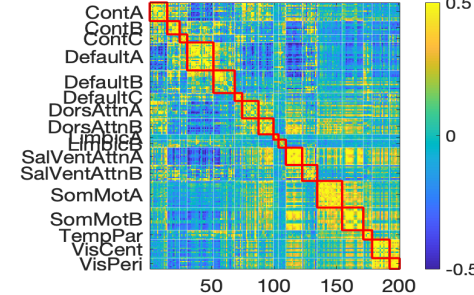
Traditional node-based “view”
(about 0.2 Hz)



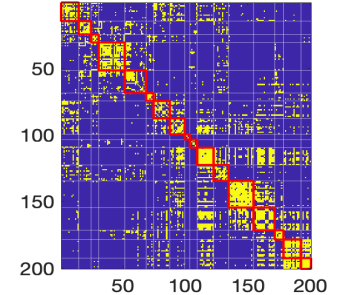
BOLD time series (z-scored)



correlation matrix



thresholded matrix

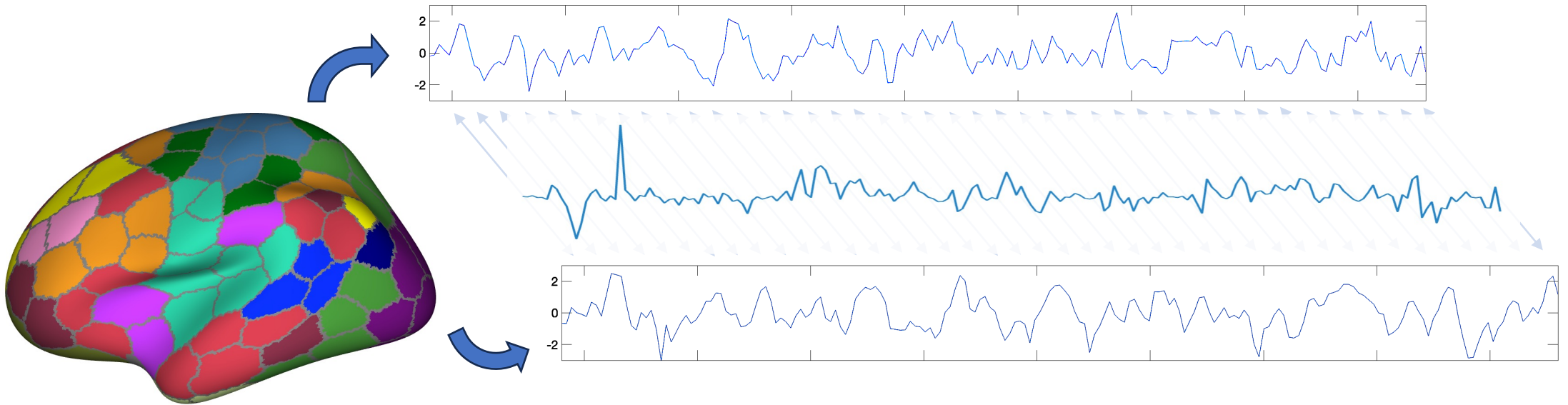


Business as usual, analyzing the nodes:

- Calculate the correlation matrix by taking the correlation between node pairs, forming a so-called connectivity matrix of time-averaged similarities
- Possibly threshold this matrix, to preform graph-theory analyses...

Calculating Edge Time Series

Take the element-wise multiplication between node time series...

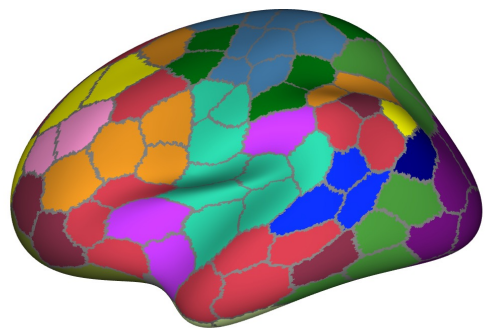


The **“edge time series”** records the instantaneous agreement between two node time series

- *When two nodes have high values, they multiply to form a high-amplitude spike*
- *When one or both nodes near zero, they produce low amplitude values*

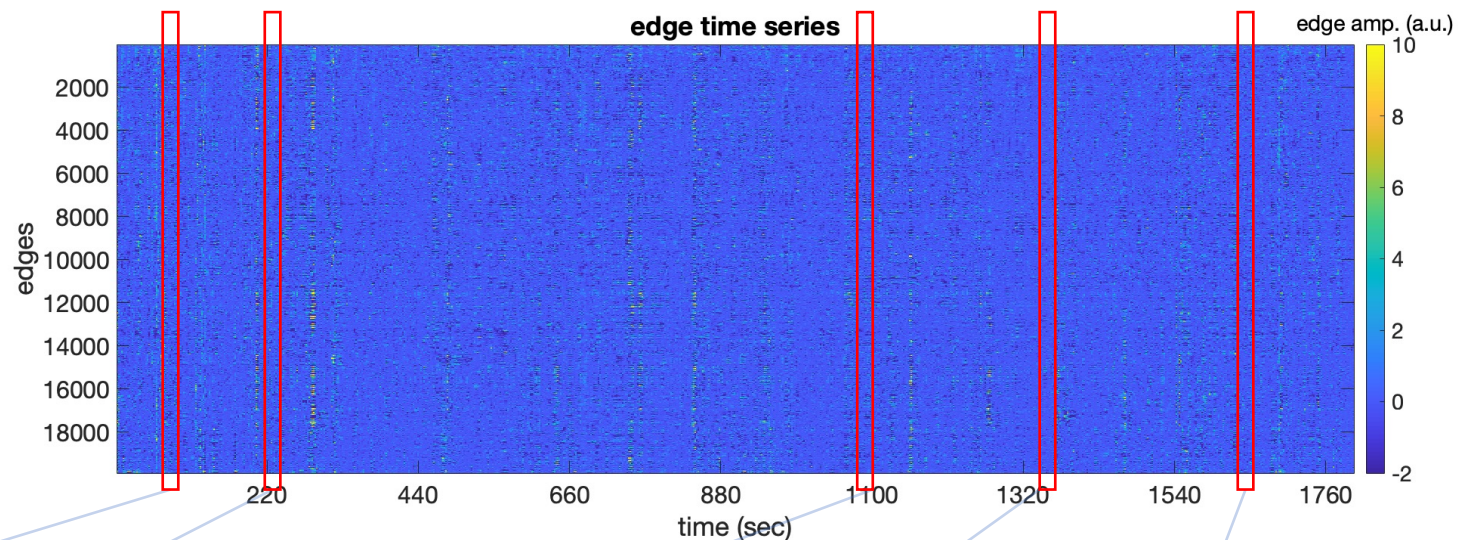
Edge time series are an intermediate step of traditional Pearson correlation equation

- *Mean of the edge time series (across time) is exactly Pearson r value*

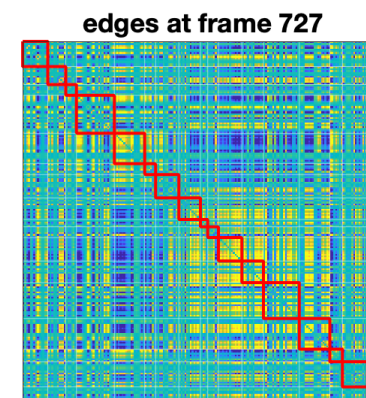
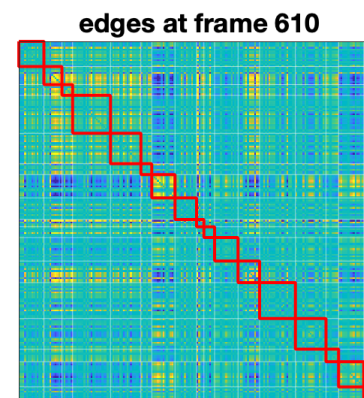
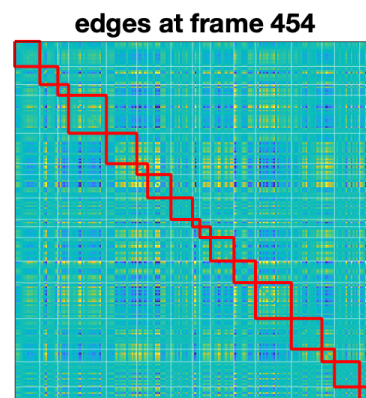
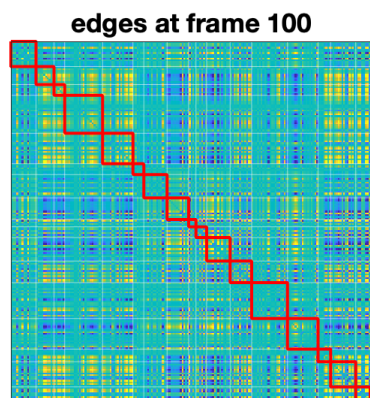
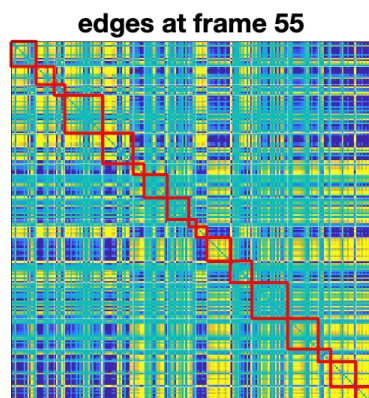


for 200-node
parcellation

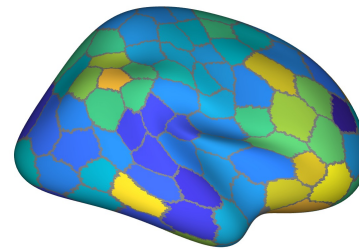
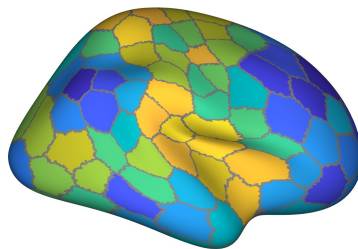
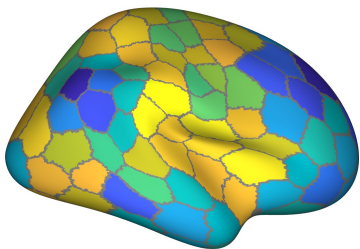
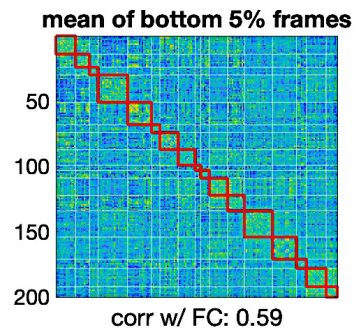
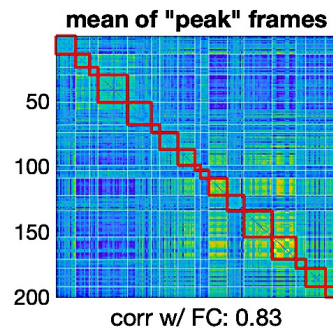
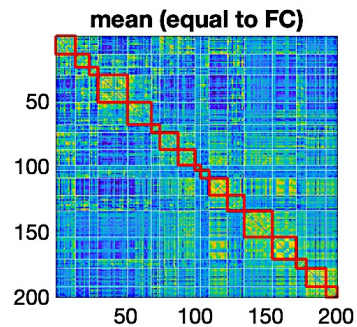
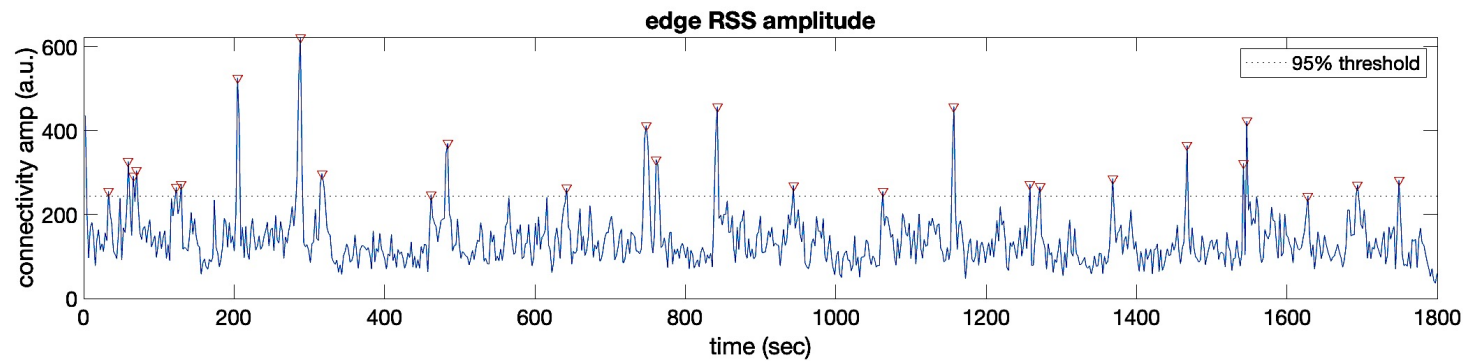
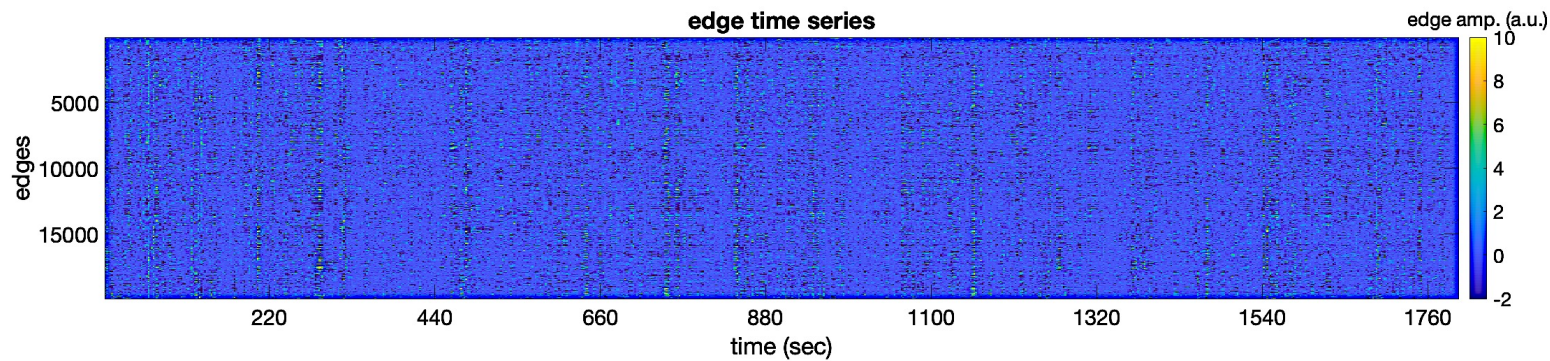
$$\text{edges} = \frac{200 \times 199}{2}$$



At each time point, we get a picture of the instantaneous
similarity of the brain



Similar to sliding-window connectivity analysis, but window is size 1

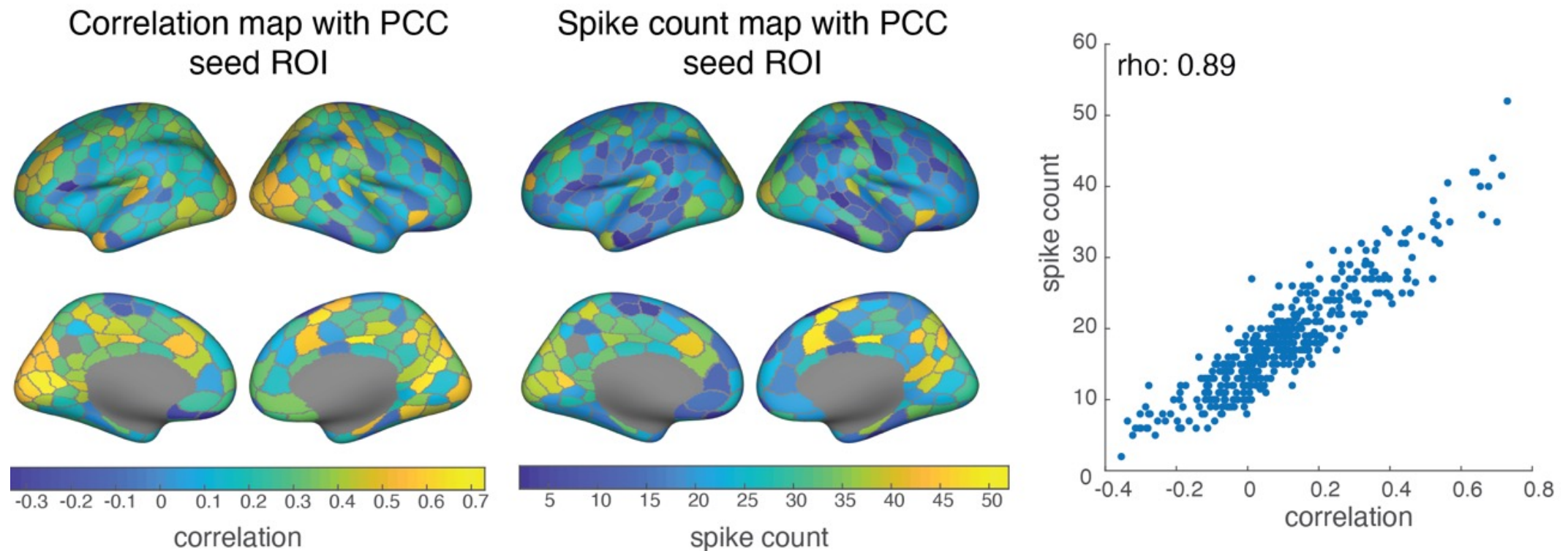


By taking the instantaneous similarity in a small fraction of the timepoints **(3.3%)**, we can reconstruct broad-scale FC organization

Suggesting that FC organization is expressed in **punctate events**

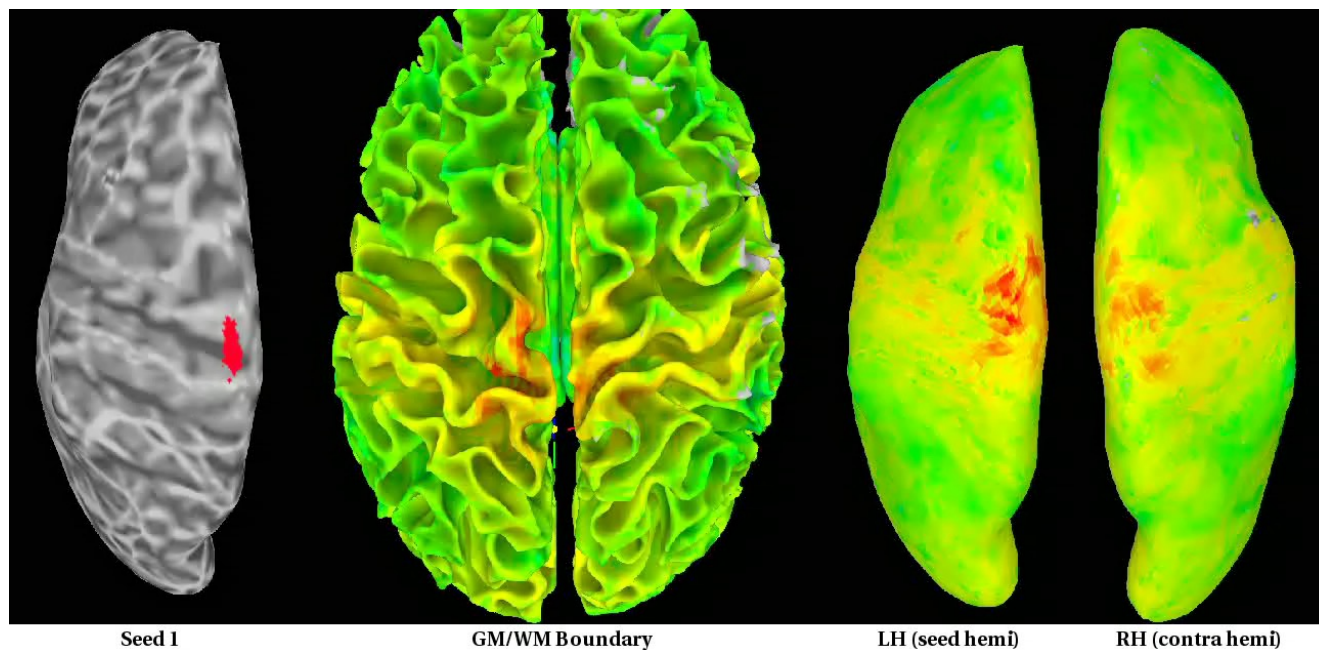
Connectivity simplified:

- Binarize edge time series into spike/no spike and count the number of high amplitude events.
- **Minimal information loss after discarding continuous information.**
- Reaffirming (e.g., point processes, CAPS) **the punctate nature of connectivity.**

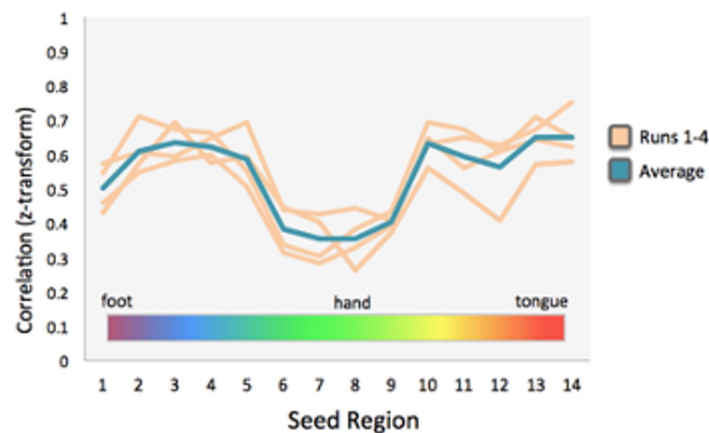
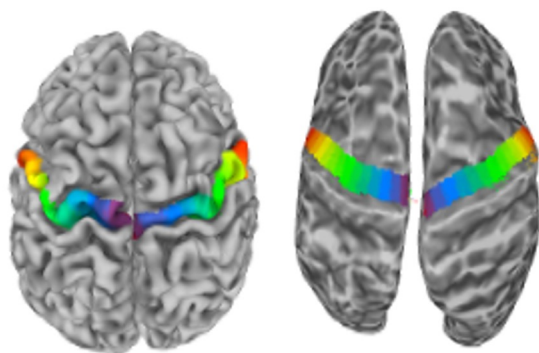


Mysteries

- Why does the BOLD response (activation -> blood hyperoxygenation) happen?
- What are the neuronal/hemodynamic mechanisms behind BOLD transients, nonlinearities, inhomogeneities?
- Is inhibition vs excitation differentiable?
- What are the sources and types of spontaneous fluctuations and connectivity? What is the global signal?
- What is the purpose of resting state fMRI?
- What are we missing in activation? Simple regressors, low sensitivity, large/fixed parcellations...
- Why is the parcellation size what it is? Are there finer natural parcellations? What is meaningful?
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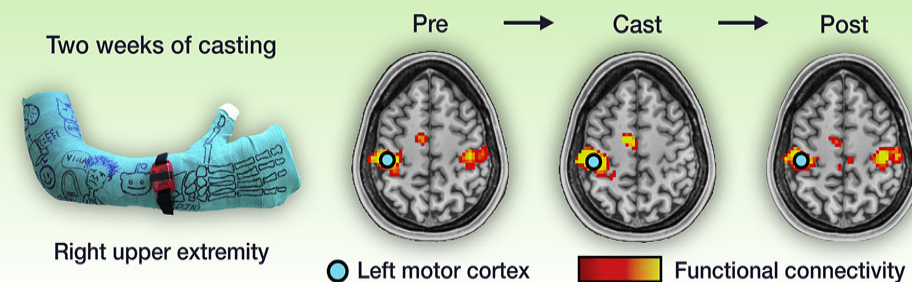


Motor cortex mostly in left-right sync, but hands are not

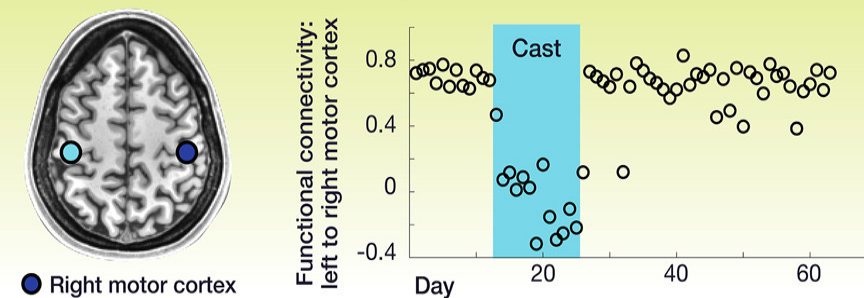


Unconscious Processes

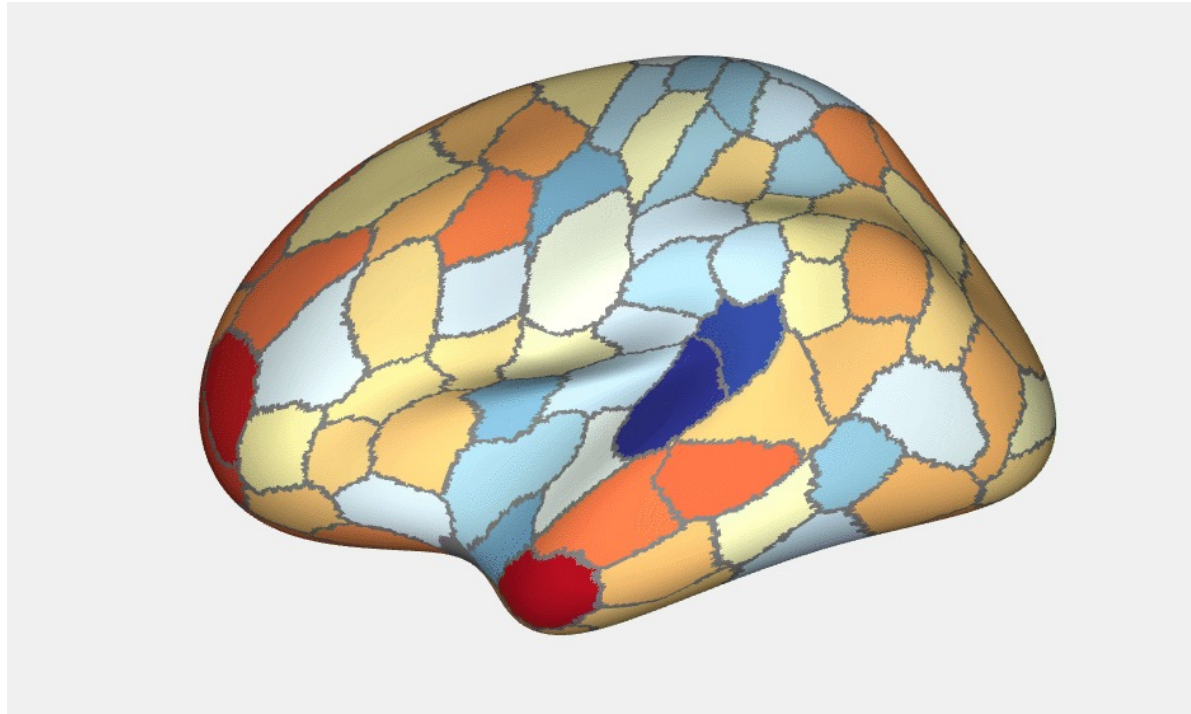
Disuse of brain circuits causes functional disconnection



Functional disconnection begins within hours to days



D. J. Newbold et al. Neuron, 2020



“...we posit that the low dimensionality of spontaneous neural patterns may reflect slow transitions between generic priors tuned for **low dimensional, general-purpose, behavioral patterns**. Itinerant dynamics across sequences of brain states may reflect the **exploration of the brain’s dynamic repertoire** ... to remain flexible.”

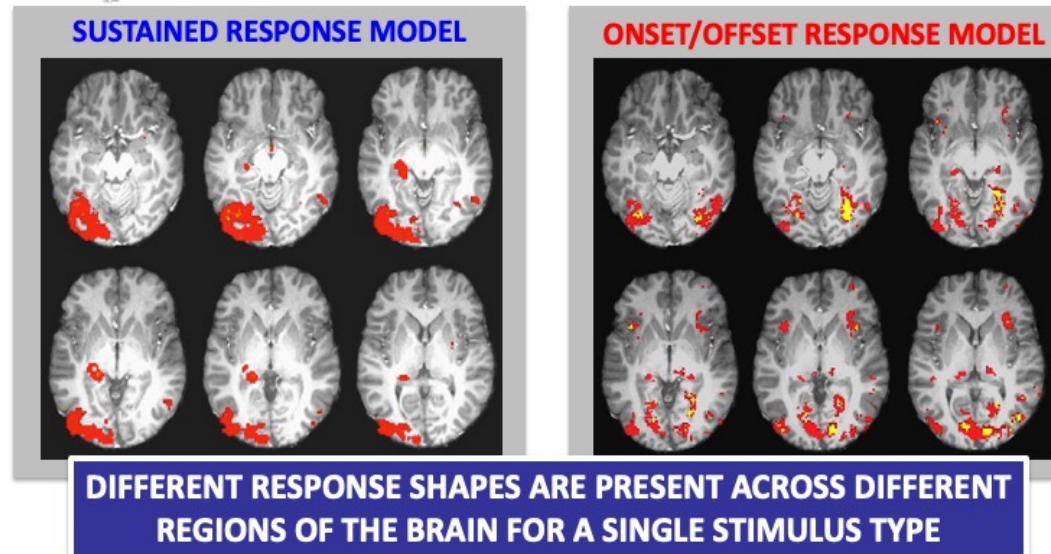
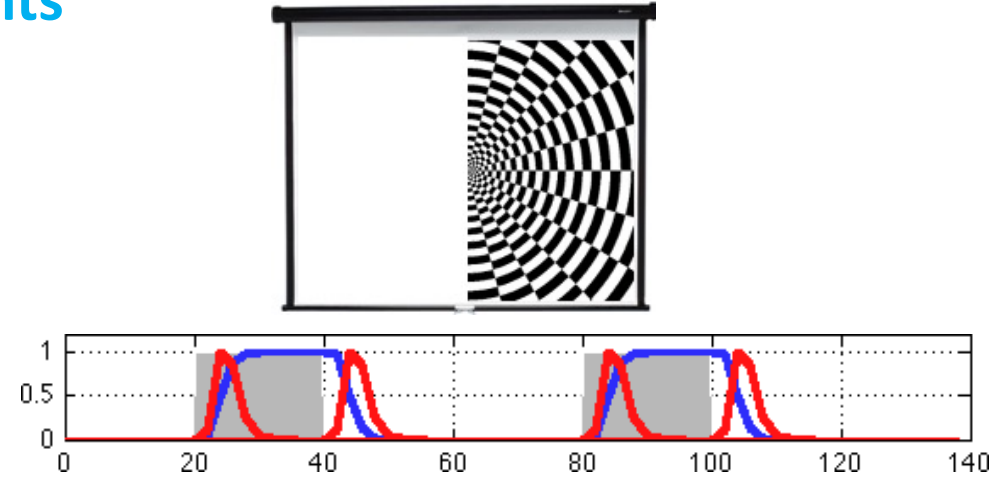
G. Pezzulo et al. TICS 2021

It also may be that our “stream of consciousness” or spontaneous conscious thoughts are driven by this same fundamentally unconscious process.

Mysteries

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Modeling Transients



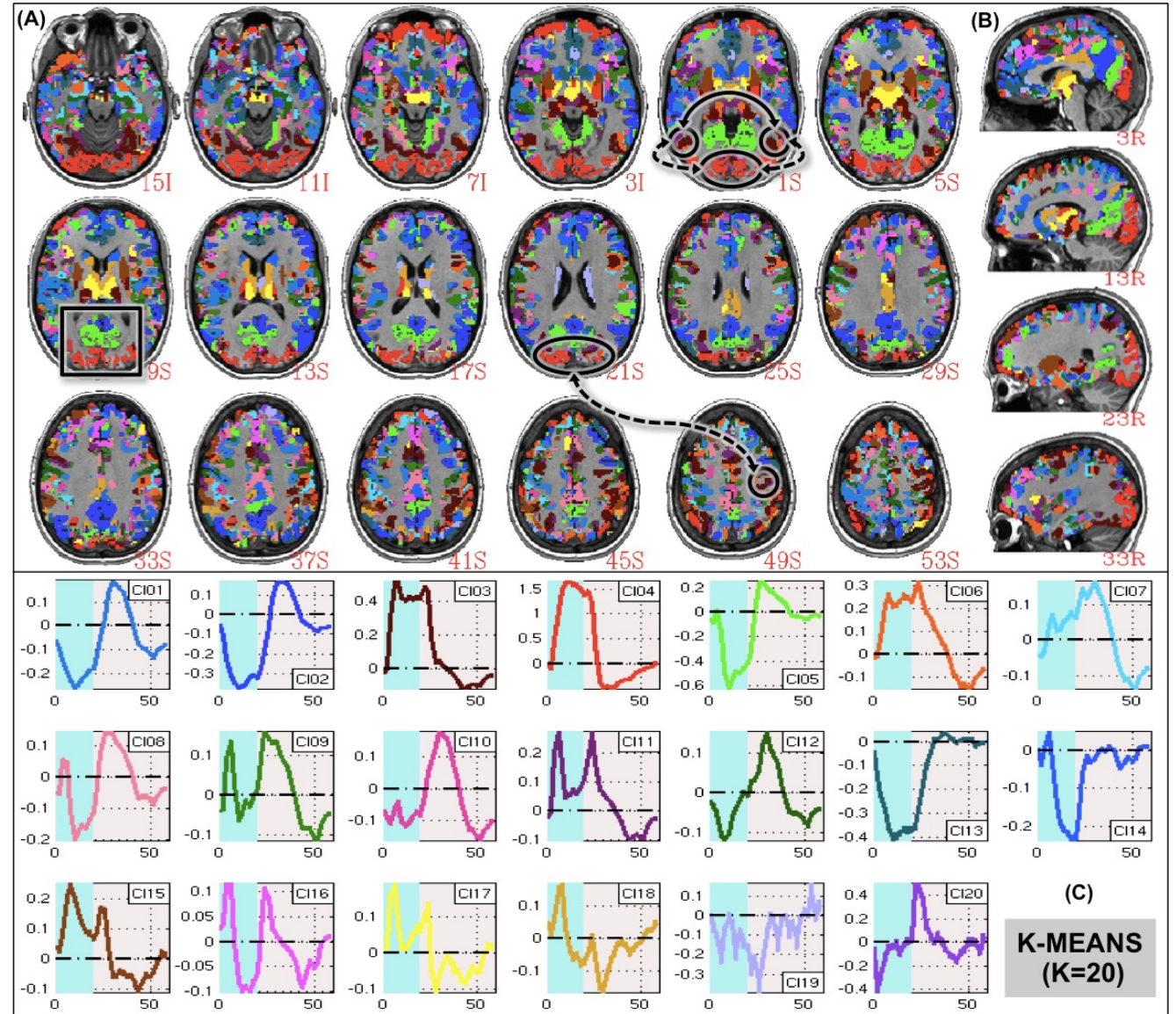
Uludag et al. Magn Reson Imaging, 26, 863-9 (2008).

9 Hours of Averaging with Unconstrained Model

K-means clustering of all time-locked signal

Simple full field checkerboard with
word/letter discrimination task

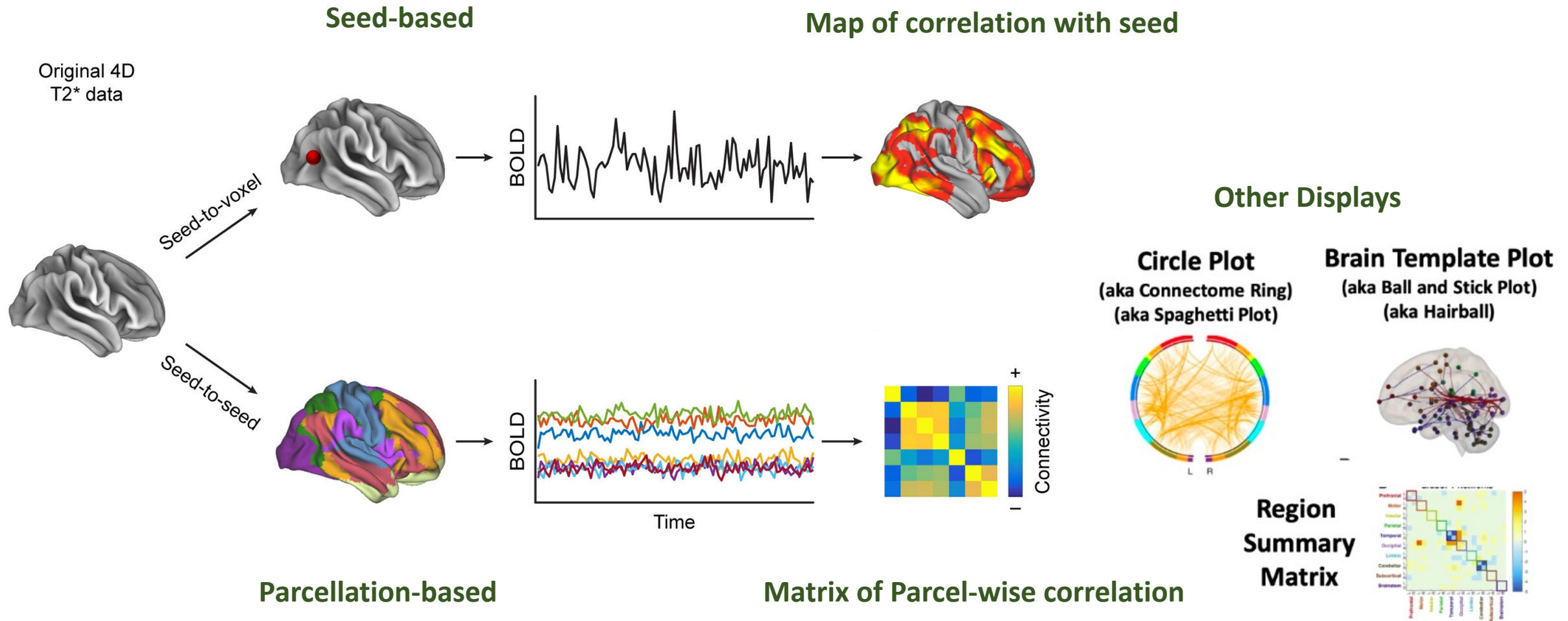
Interpretability requires a model
However, any model may miss salient data.



Mysteries

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- What are the neuronal/hemodynamic mechanisms behind BOLD transients, nonlinearities, inhomogeneities?
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- Best way to compare brains across/within groups and across individuals at different resolutions?
- How relevant is the spatial/temporal scale of fMRI for deriving principles of functional brain organization?

Approaches to connectivity analysis and visualization



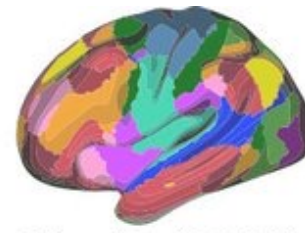
Diverse Functional Parcellation Approaches

Heirarchical clustering
K-means clustering
Ward's linkage
Region growing
Euclidean distance
Principle Component Analysis
Spectral clustering
Eigenvector discretizing
Resting state boundary maps
...

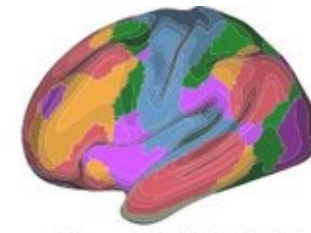
<https://biomedica.doc.ic.ac.uk/brain-parcellation-survey/>



Glasser (2016)



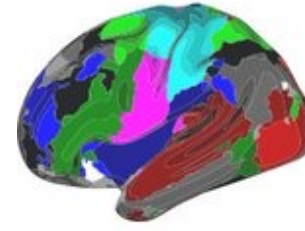
Yeo17 (2011)



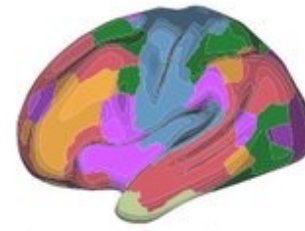
Yeo7 (2011)



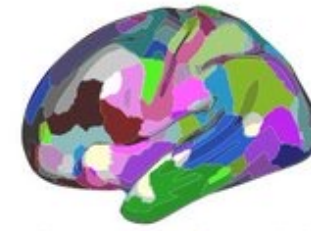
Power (2011)



Yeo (2015)



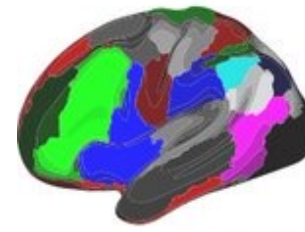
Schaefer (2018)



Gordon (2016)



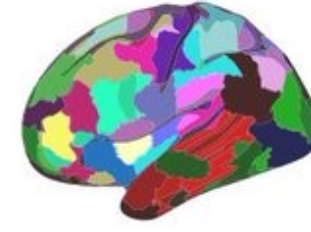
Fan (2016)



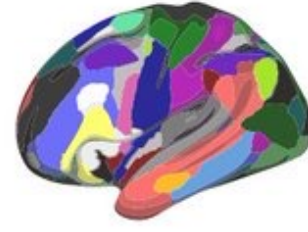
Arslan (2017)



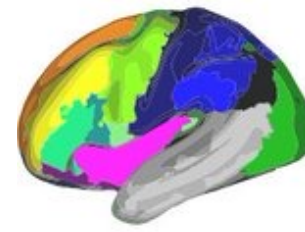
Baldassano (2015)



Shen (2013)



ICA



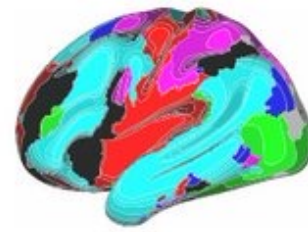
AAL



Desikan



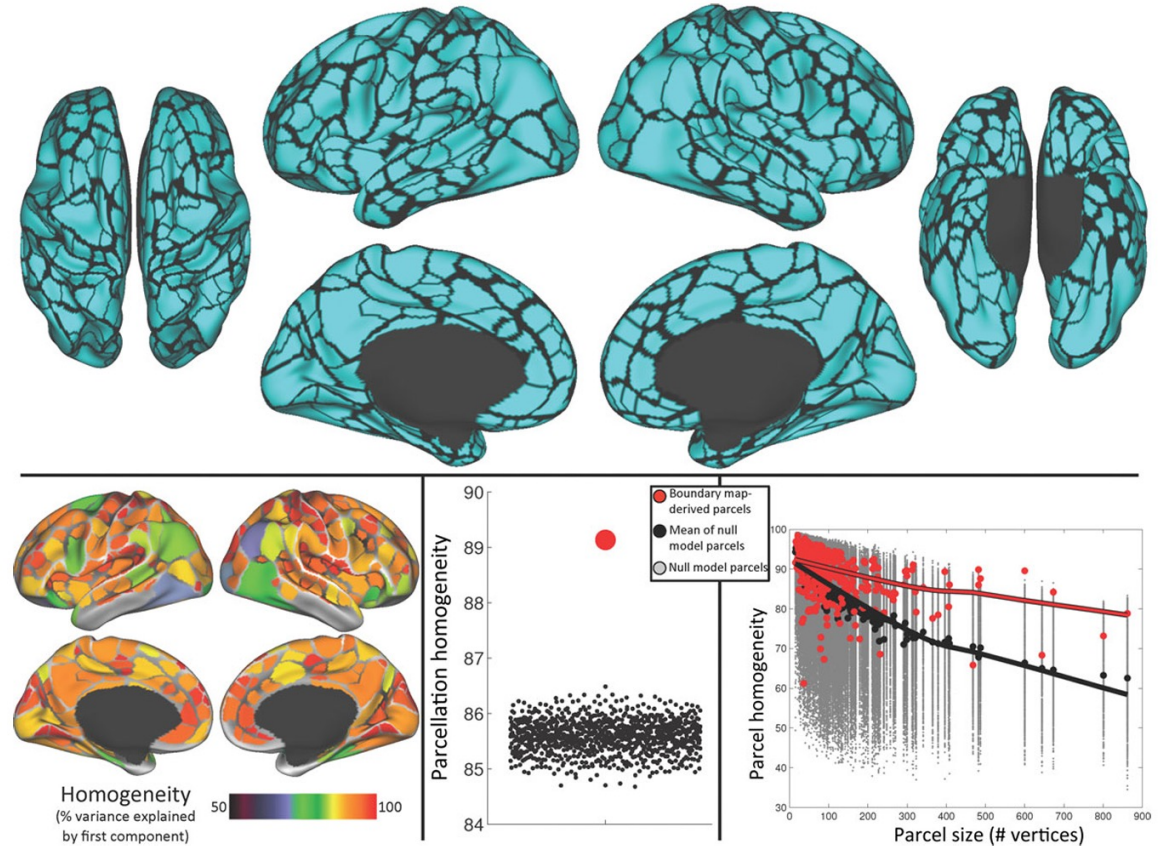
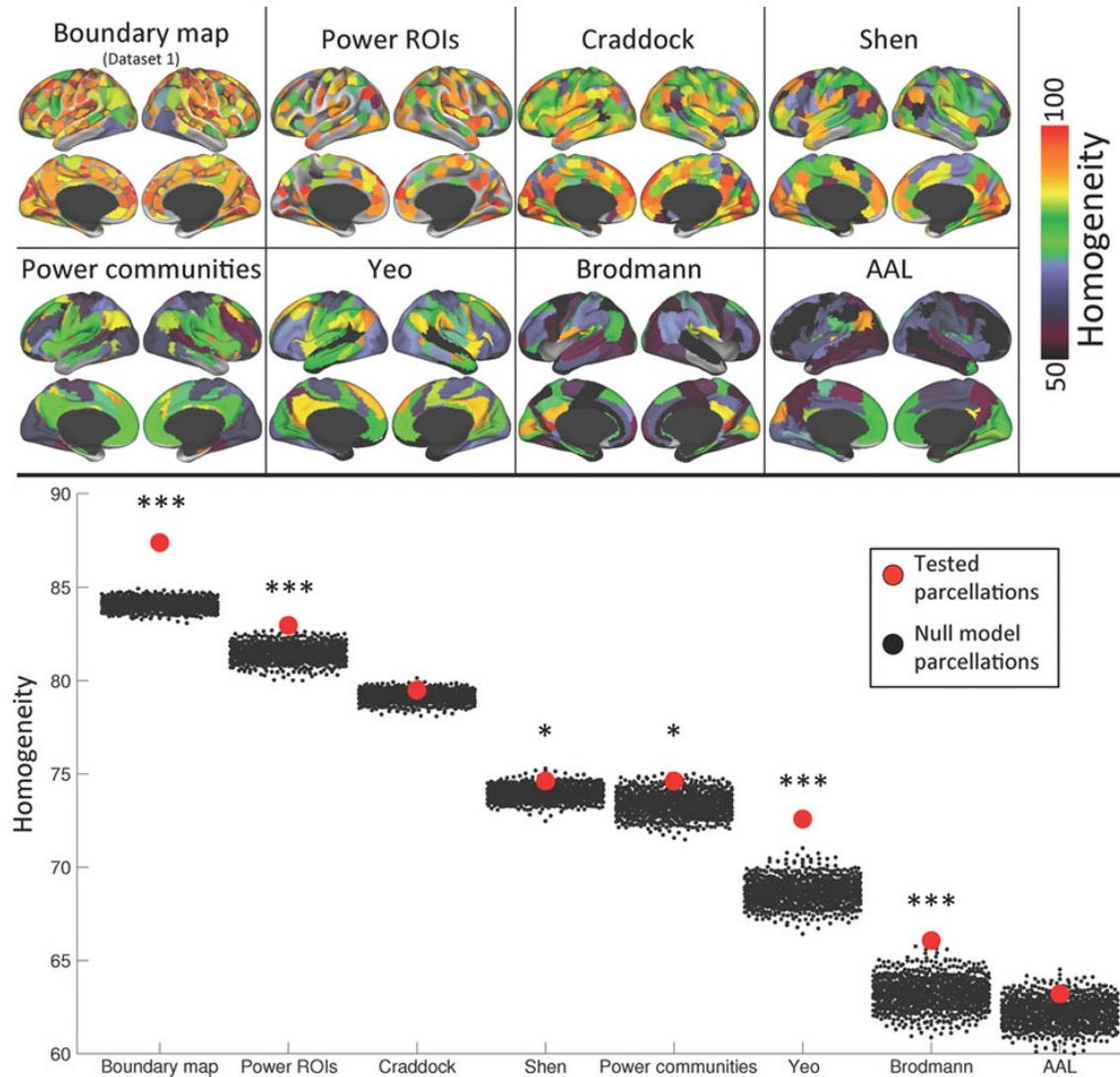
Dextrieux



MDTB7

Parcels vary in the fidelity that they capture nodes

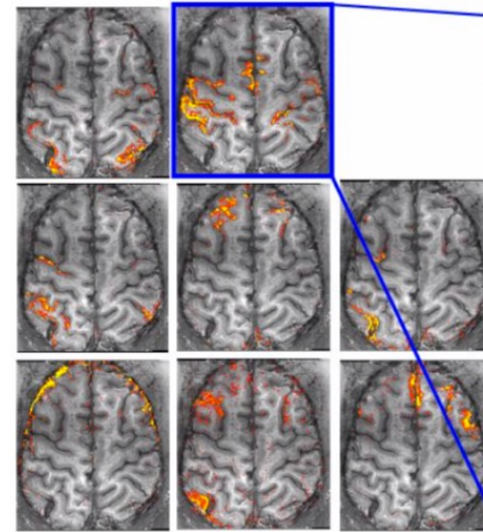
Homogeneity: Variance explained by first PCA



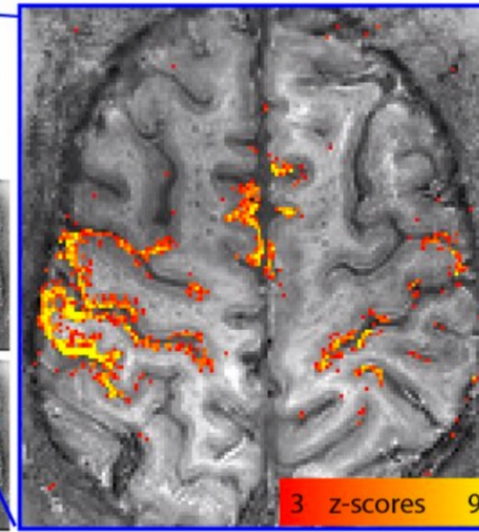
E. M. Gordon, et al. "Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. Cerebral Cortex, 26, 2016

Iterative ICA decomposition of the *resting state* VASO signal.

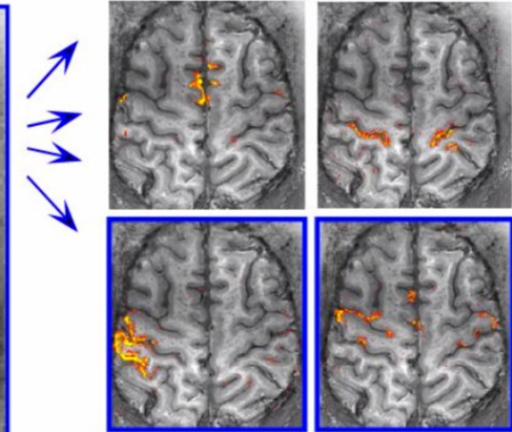
A) 8 example ICA components



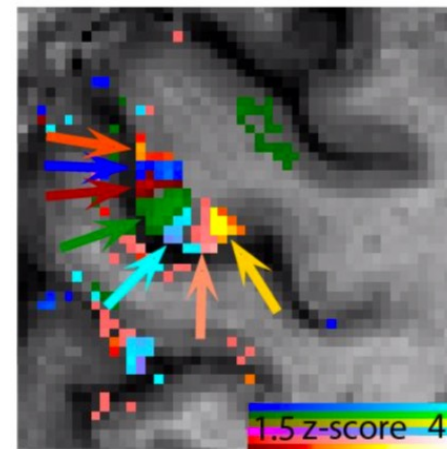
B) zoomed view of sensorimotor network



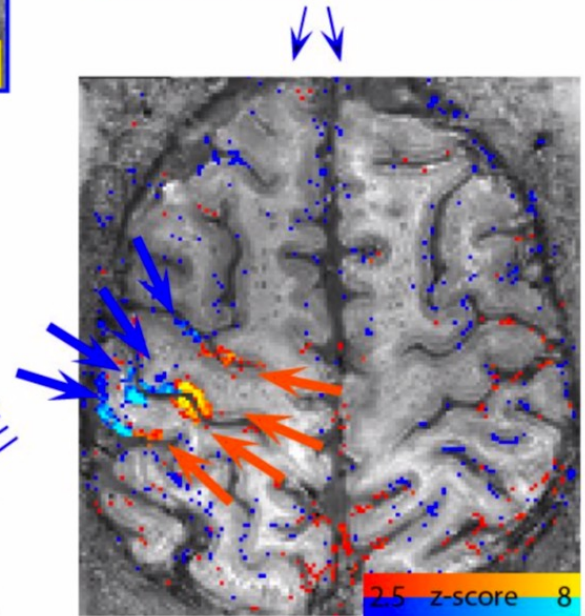
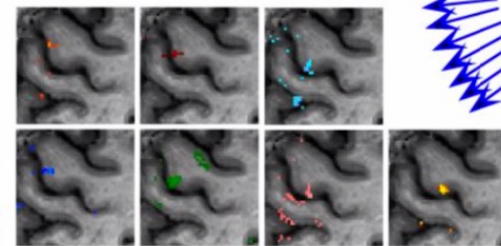
C) sub-components of sensorimotor network



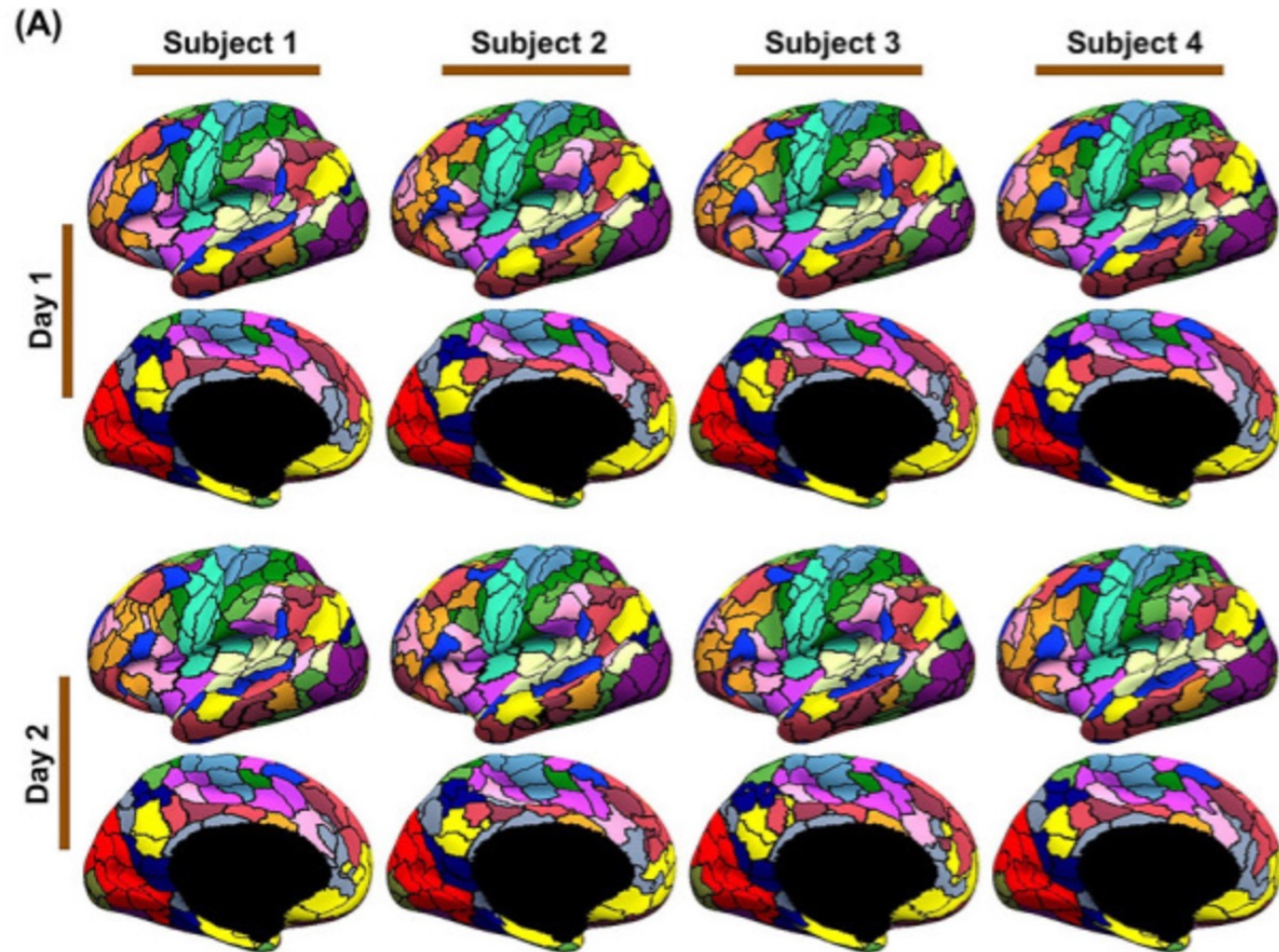
D)



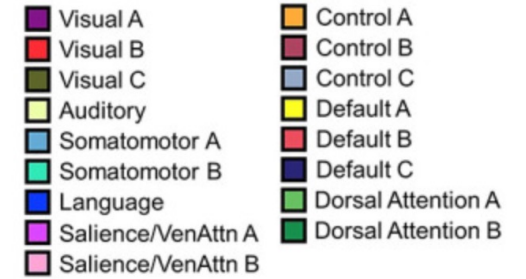
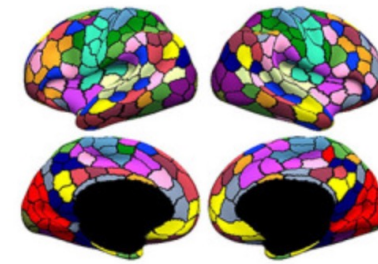
sub-components of hand knob:
7 separate 'columnar' components can be extracted



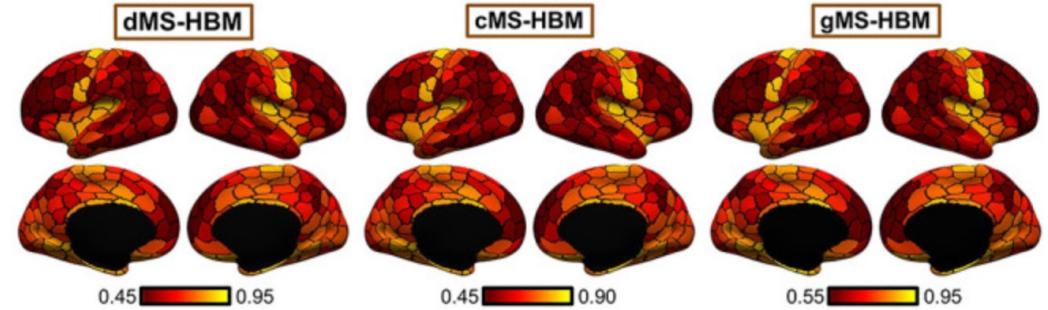
Each Individual Parcellation is Unique



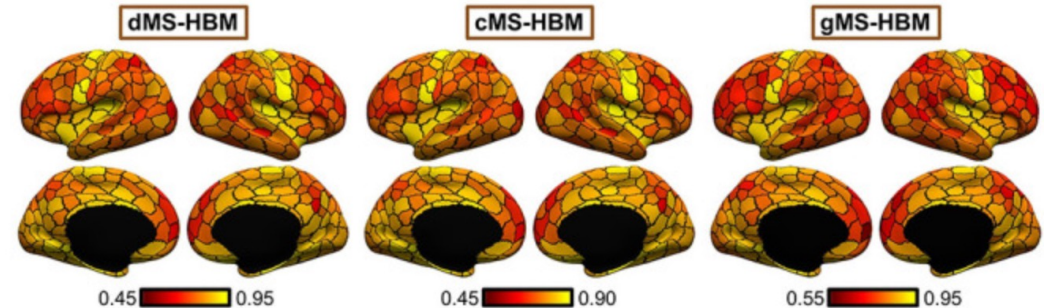
(A) Group parcellation

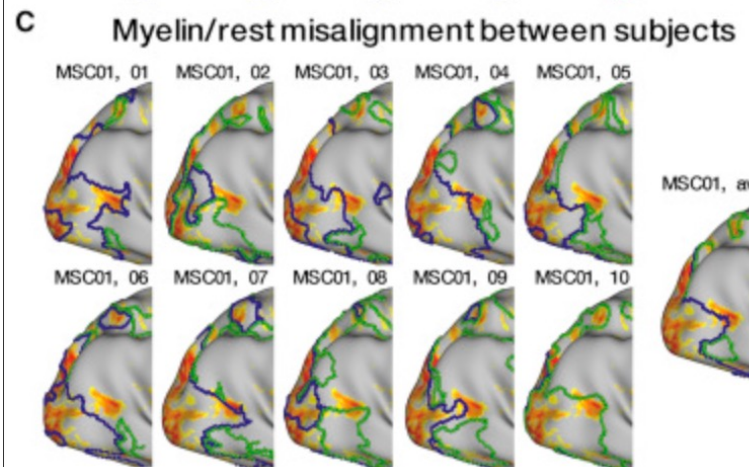
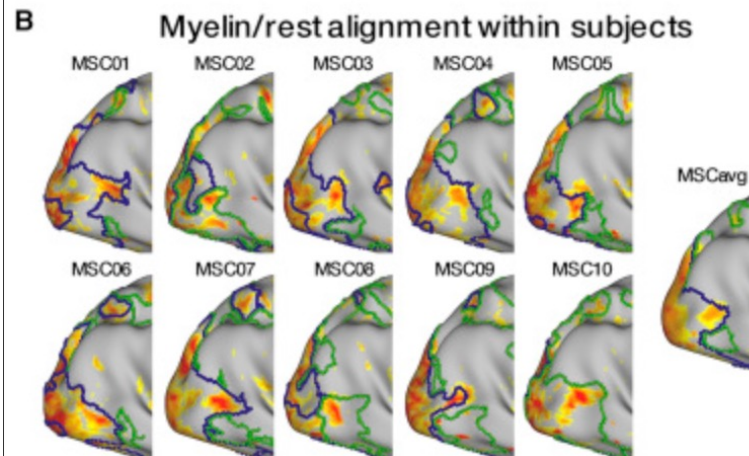
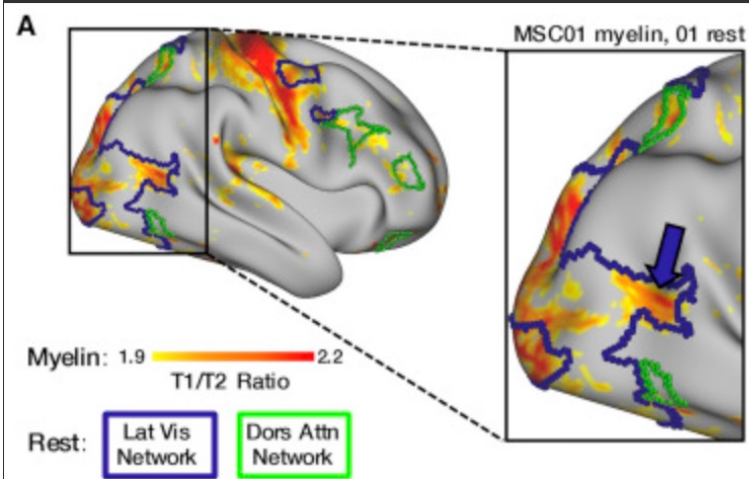


(B) Inter-subject similarity



(C) Intra-subject reproducibility





- Myelin Density Maps T1:T2 ratio > 1.9
- Functional Connectivity Maps

- Large Structural Variation among Subjects
- However, resting state functional connectivity aligns with Myelin Density Landmarks

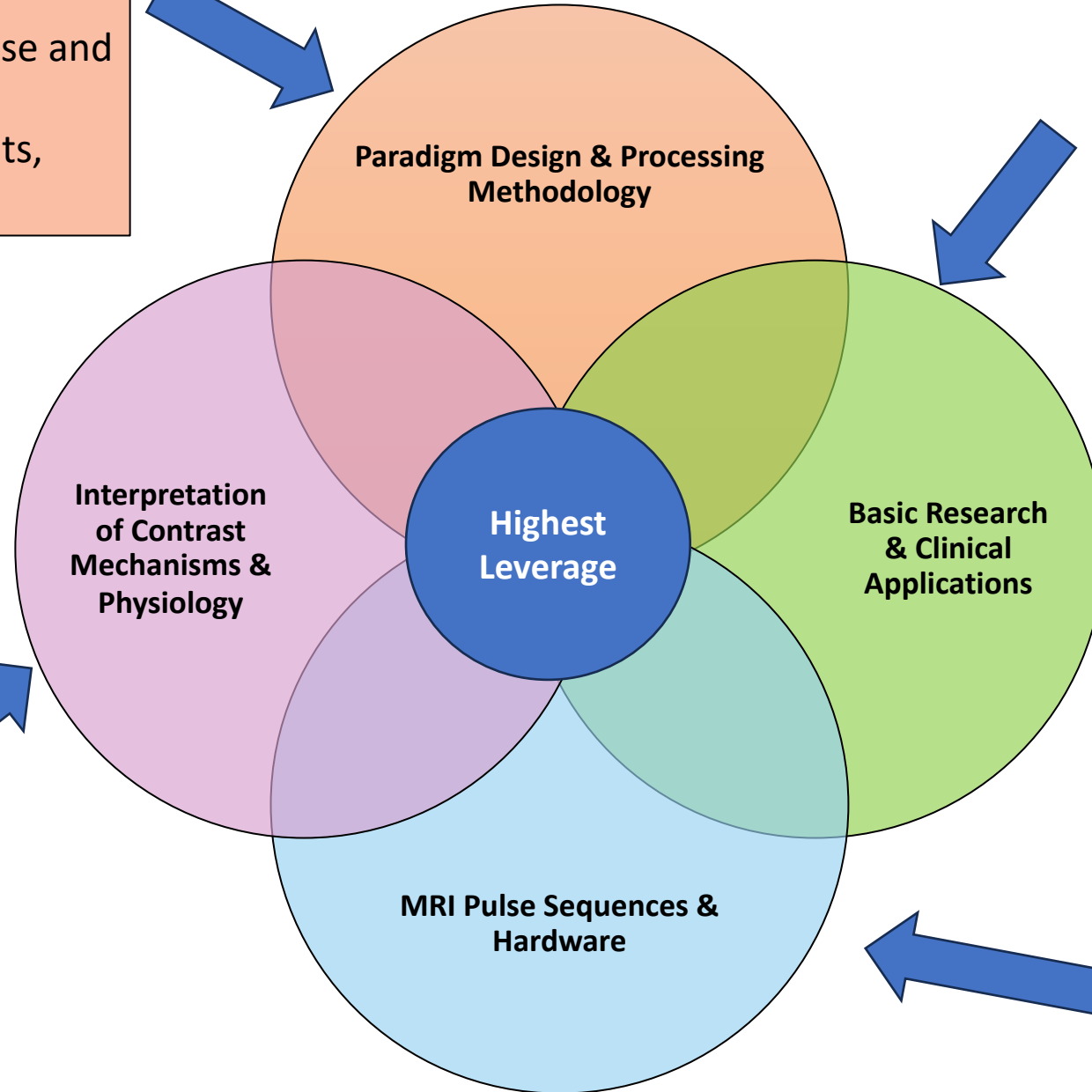
Challenges of fMRI

Not a controversy or mystery, but rather a direction we want fMRI to go without a straightforward means to get there.

FMRI "Pillars"

- Capture neuronal activity, patterns, dynamics in time and space.
- Separate information from noise and artifact.
- Compare states, individual traits, and groups.

- Biomarker discovery and development
- Targets for neuromodulation
- Presurgical mapping
- Neurofeedback
- Uncover mechanisms and principles of functional brain organization.



- Speed
- Resolution
- Sensitivity
- Specificity
- Reproducibility
- Quantitation
- New Contrasts

- Identify relevant temporal and spatial structure.
- Multi-modal assessment: Relate signal to neuronal activity and non-neuronal measures.

Challenges

- Seamless data/code pooling and sharing
- Removal of ALL non-neuronal noise.
- Spatial normalization of BOLD signal weighting variation across brain.
- Real time assessment of ongoing state: fully understanding resting state
- Clinically useful “biomarkers”
- Practical clinical implementation
- Full individual subject characterization (similarities and differences)
- Adaptive parcellation (global hyperalignment?) – accounting for differences.
- Layer fMRI -> whole brain directional connectivity and hierarchy.
- Multimodal integration (EEG, optical, structural, vascular, fMRI)
- Subcortical fMRI and connectivity.
- Robust subcortical activity/connectivity assessment.
- Temporal/spatial resolution of 10 ms and 0.1 mm. – whole brain.
- More contrasts in the time series.
- Uniform shimming across whole brain.
- Migration from cartography to mechanistic understanding (models..)

Challenges

- Seamless data/code pooling and sharing
- **Removal of ALL non-neuronal noise**
- Spatial normalization of BOLD signal weighting variation across brain.
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Can we model and remove all non-neuronal fluctuations?

Spontaneous Neuronal Activity

- arousal
- conscious thought
- unconscious processes

Respiration

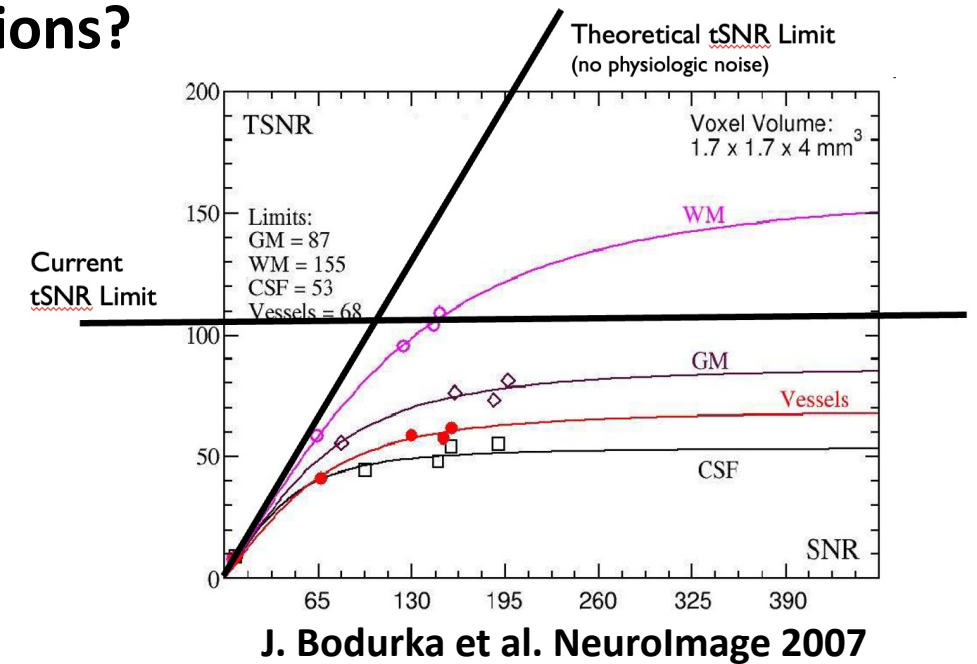
- chest wall B_0
- variable end tidal CO_2 related flow/BOLD changes

Cardiac Pulsation

Thermal Noise

Motion

Scanner Instability



Thermal Noise,
Motion, Scanner
Instability

Neuronal BOLD
Fluctuations

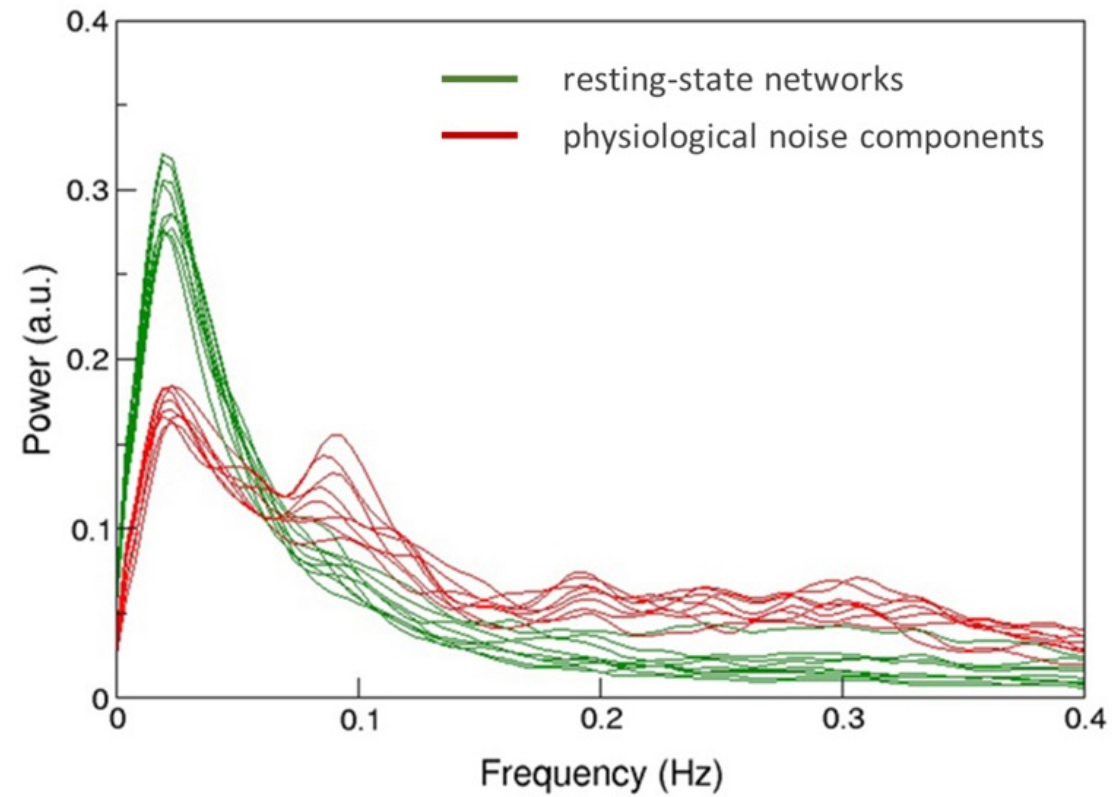
Respiration

Cardiac

Noise Removal

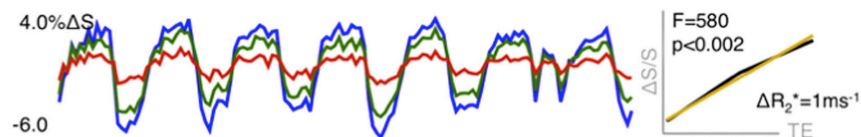
B

Power spectra of rs-fMRI signal components

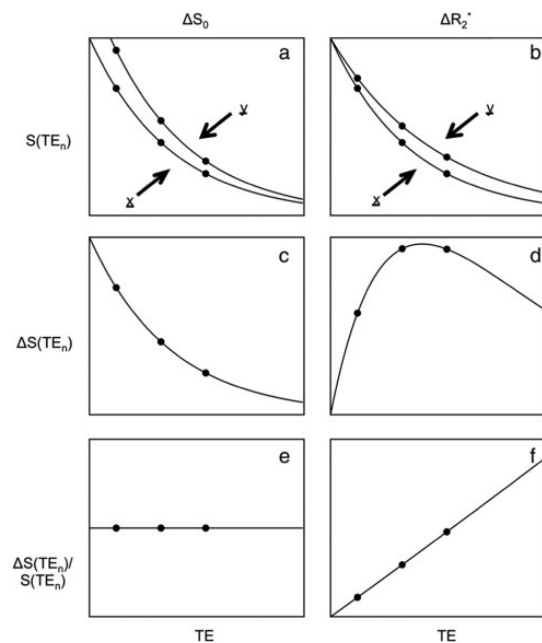
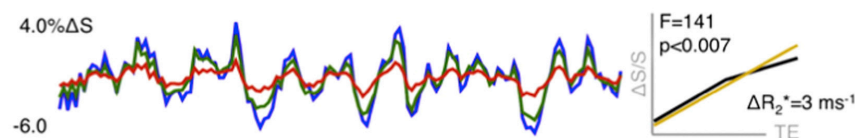


Using Multi-echo EPI to identify and eliminate non-BOLD components

Multi-echo EPI time courses for task (V1)

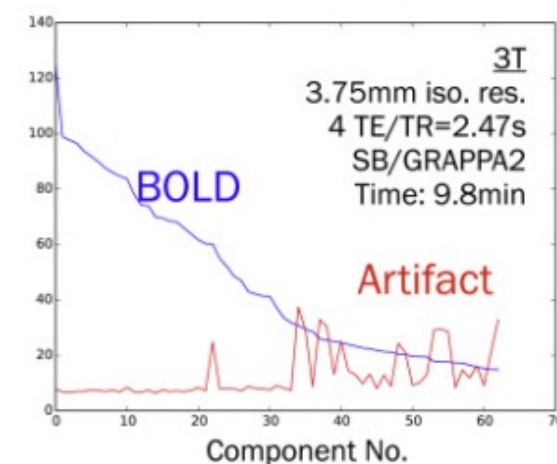
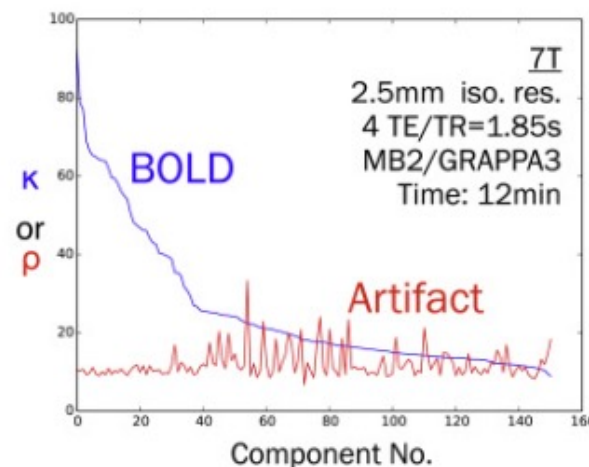
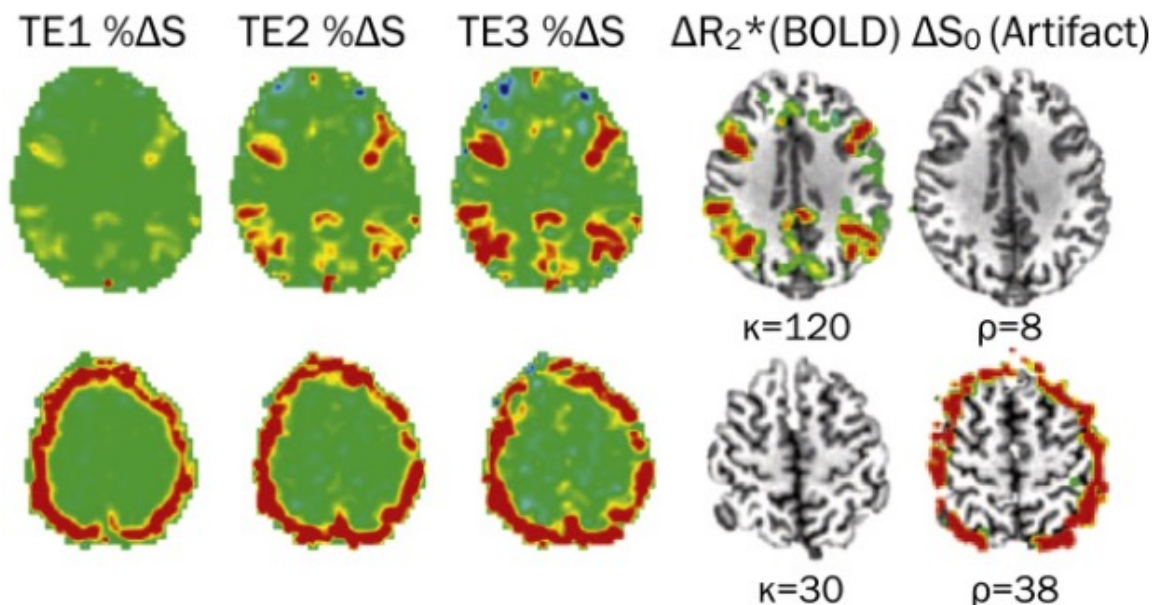


Multi-echo EPI time courses for rest (precuneus)



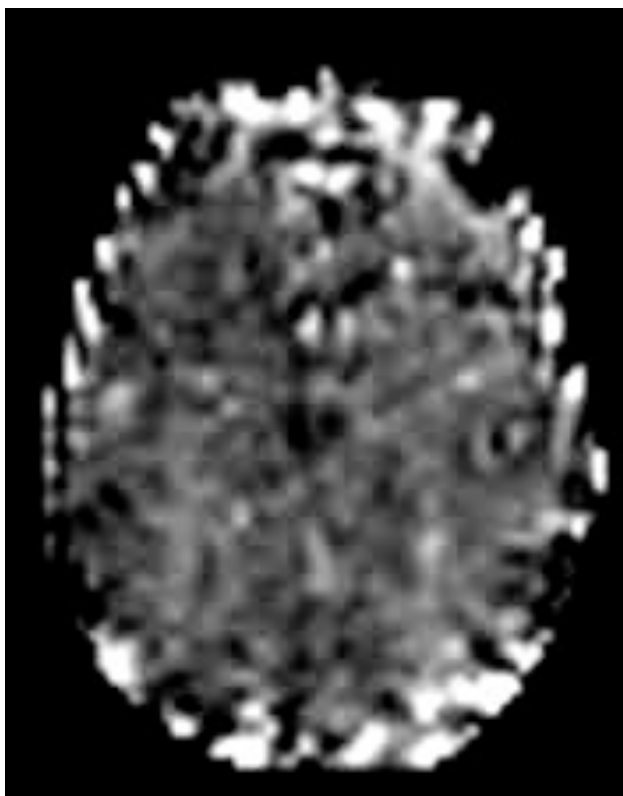
$$\text{BOLD Weighting } \kappa_c = \frac{\sum_v^V z_{c,v}^p F_{c,v,R_2^*}}{\sum_v^V z_{c,v}^p}$$

$$\text{Artifact Weighting } \rho_c = \frac{\sum_v^V z_{c,v}^p F_{c,v,S_0}}{\sum_v^V z_{c,v}^p}$$

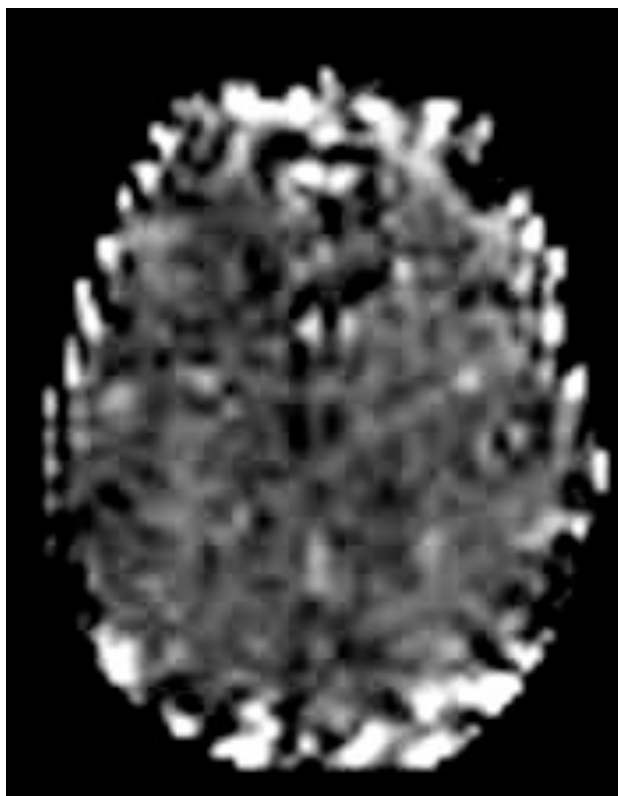


Download : [Download high-res image \(1MB\)](#)

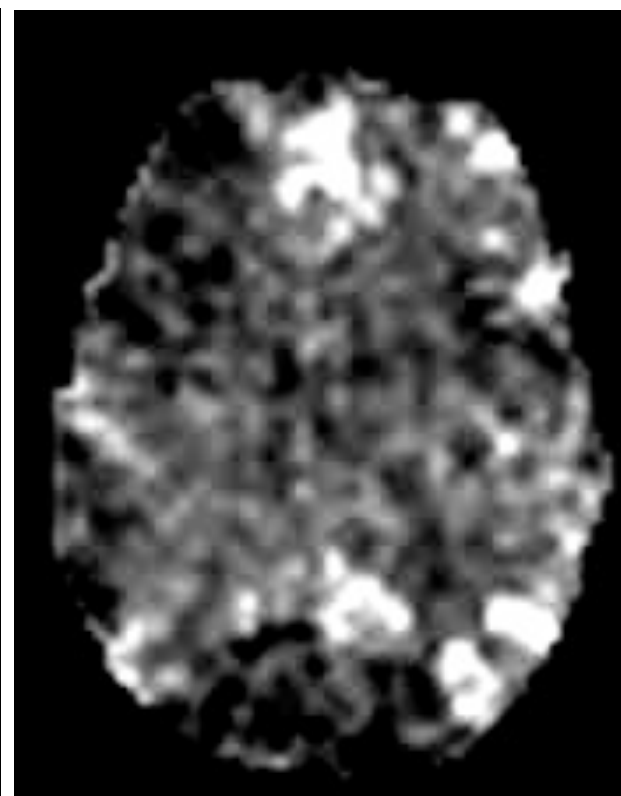
Download : [Download full-size image](#)



Raw total time series



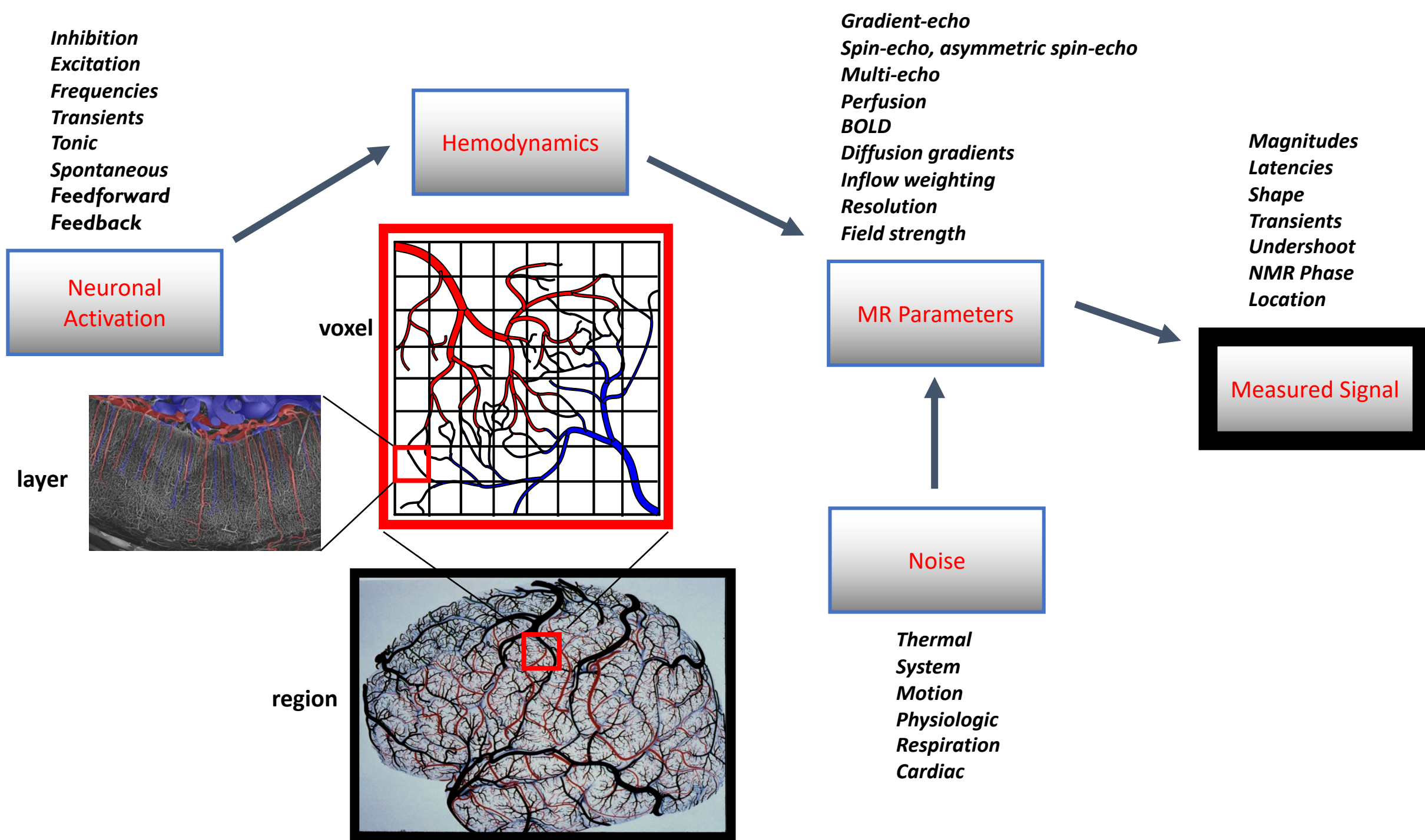
Removed time series noise

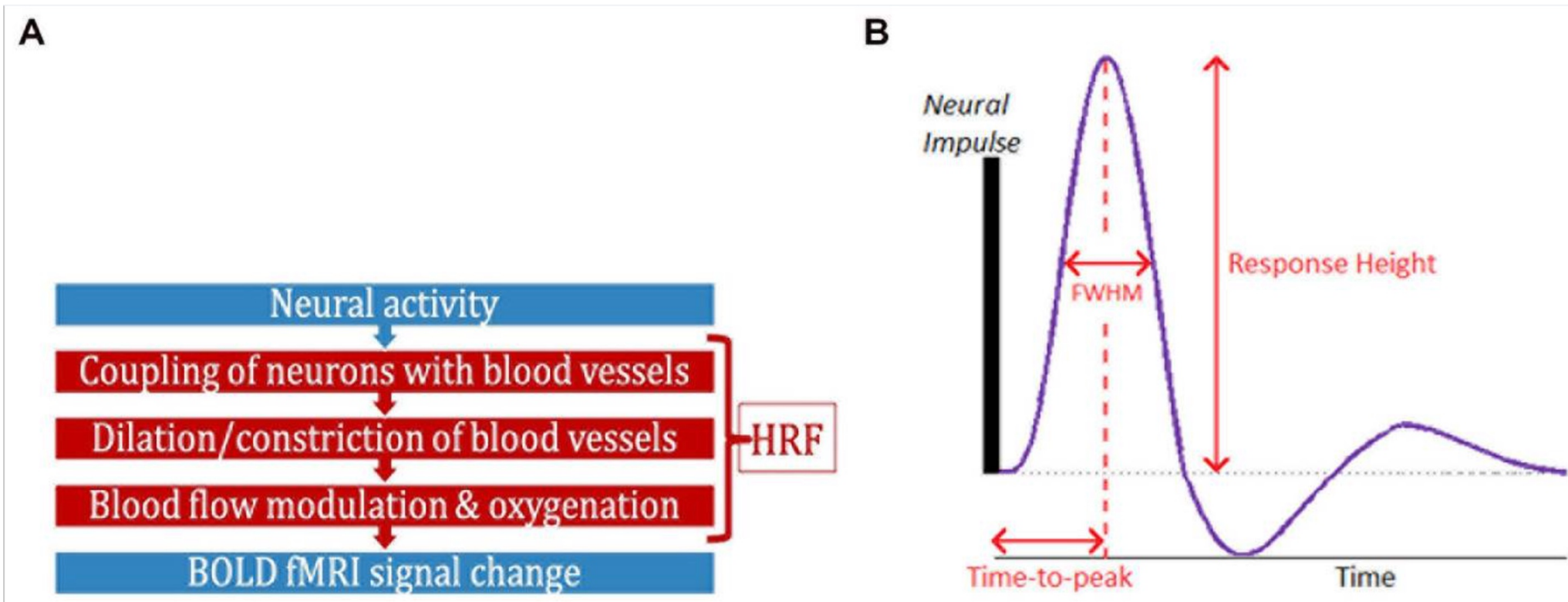


Raw BOLD time series

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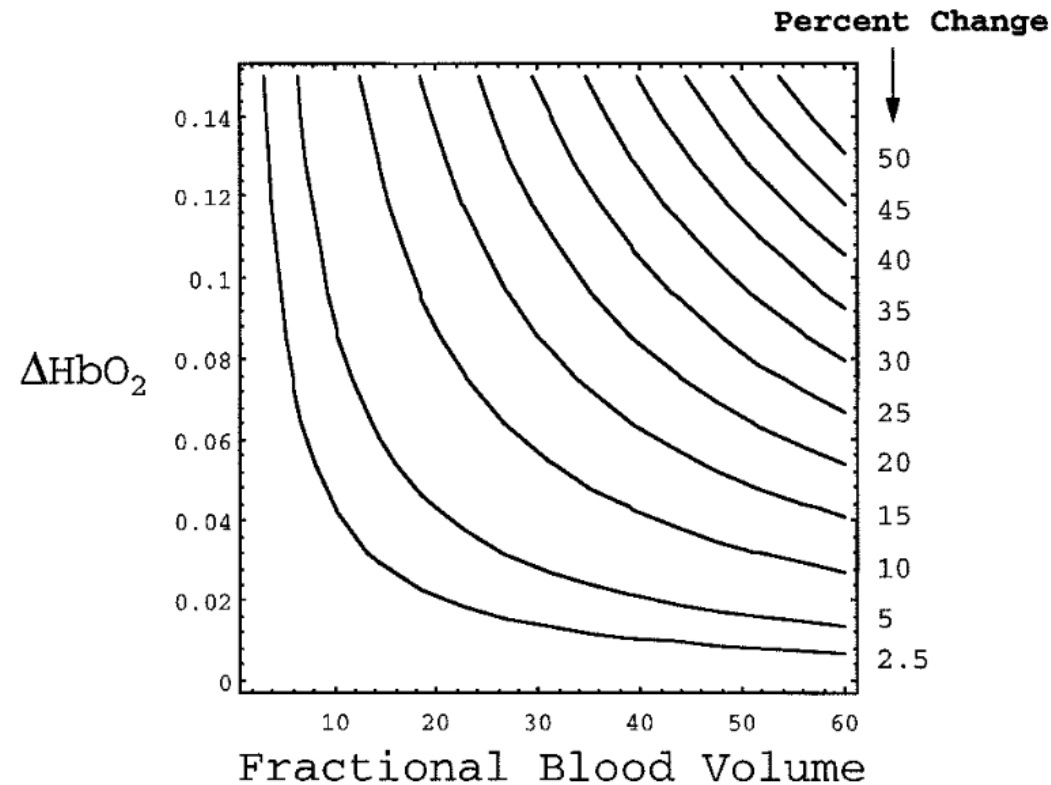
D. Rangaprakesh, et al. Frontiers in Neuroscience, 2023.

A Hypercapnia-Based Normalization Method for Improved Spatial Localization of Human Brain Activation with fMRI

Peter A. Bandettini^{1*} and Eric C. Wong²

¹ Medical College of Wisconsin, Biophysics Research Institute, Milwaukee, WI 53226, USA

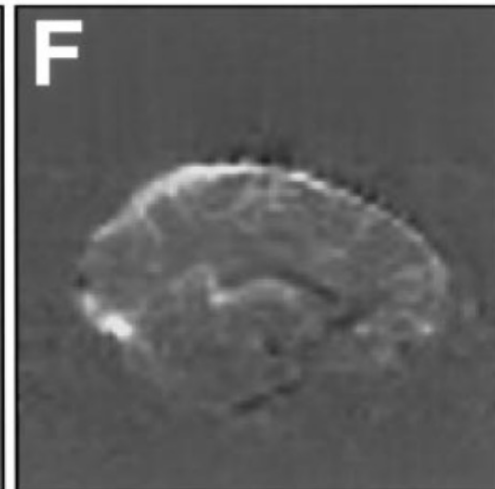
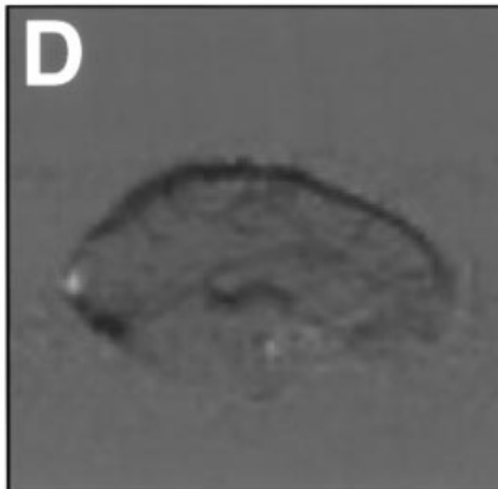
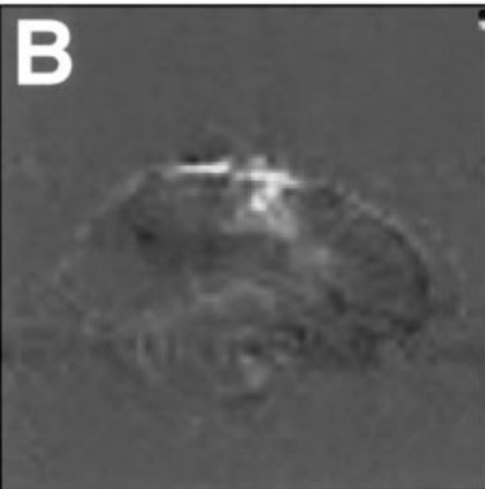
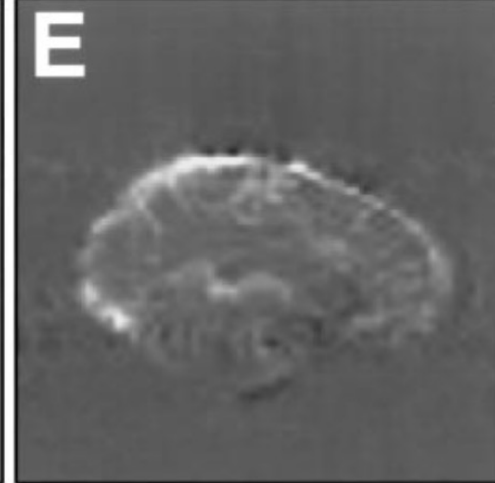
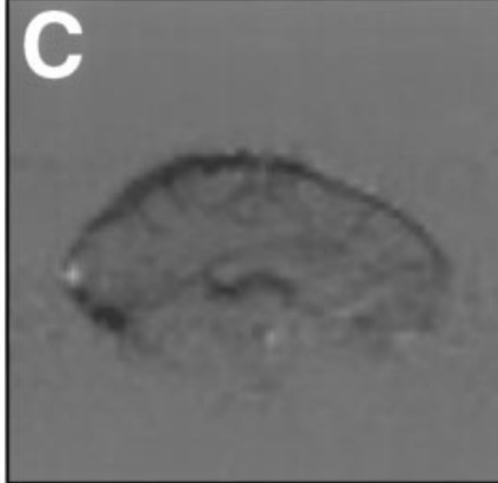
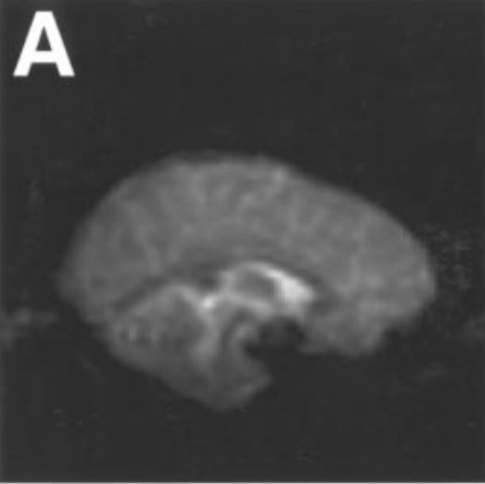
² University of California—San Diego, Departments of Radiology and Psychology, San Diego, CA 92103, USA



Anatomical

12% O₂ (Trial 1)

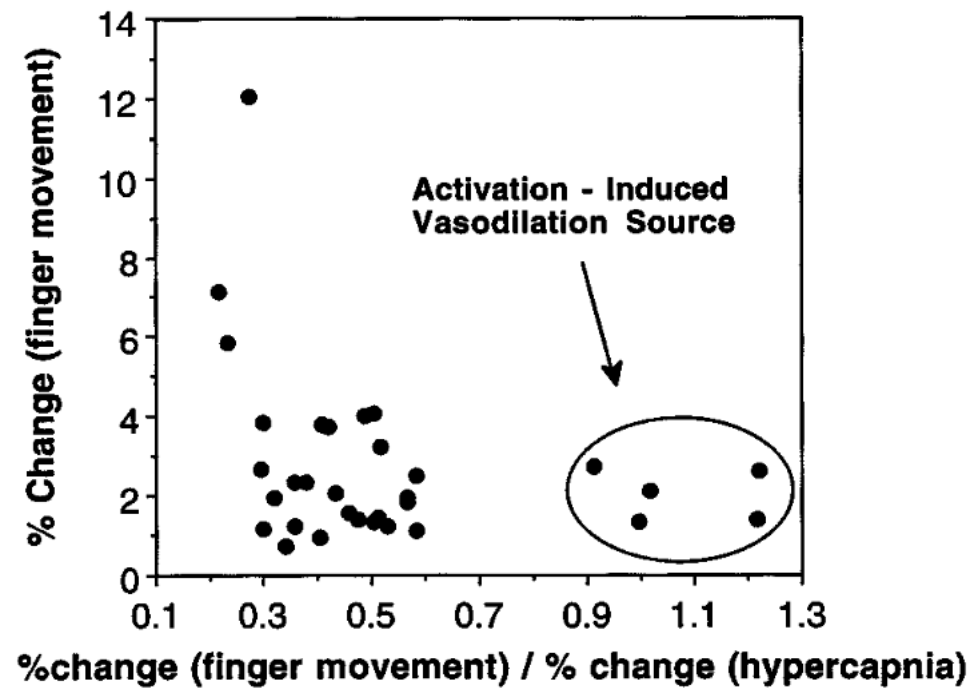
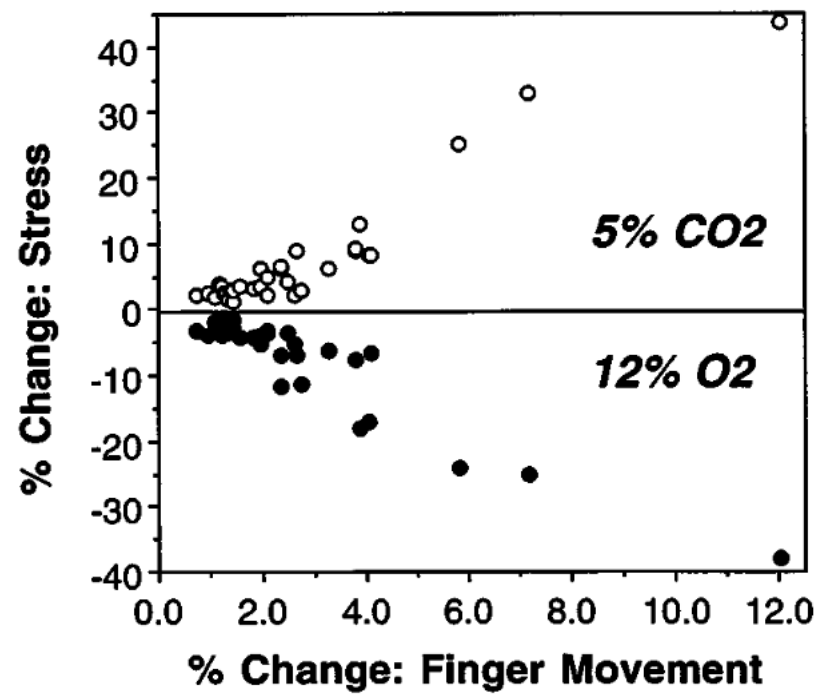
5% CO₂ (Trial 3)



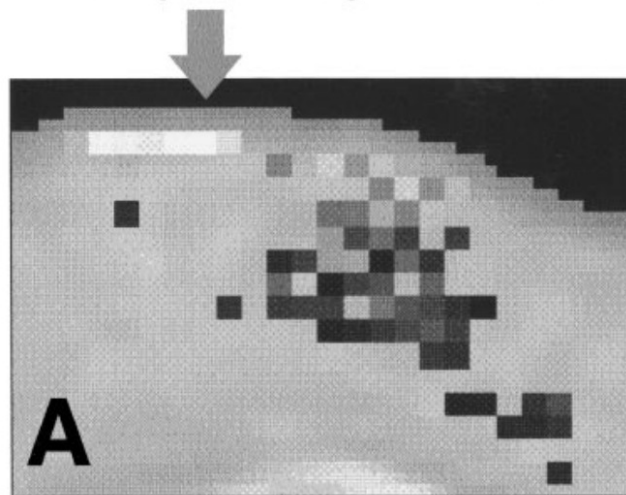
**Finger Movement
(Trial 5)**

12% O₂ (Trial 2)

5% CO₂ (Trial 4)

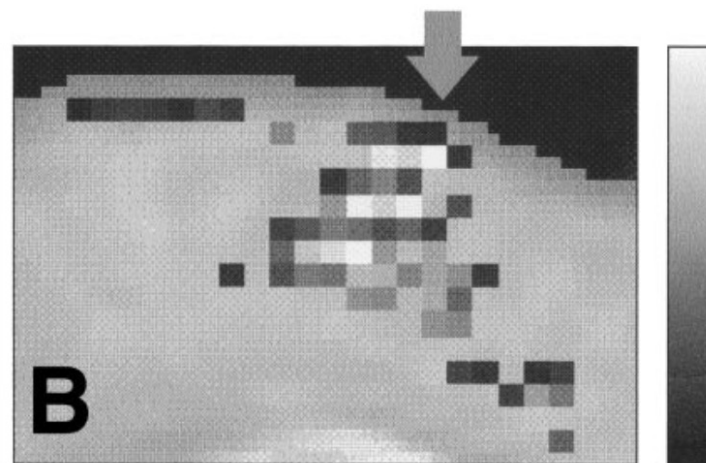


"Hot Spot" in Sagittal Sinus



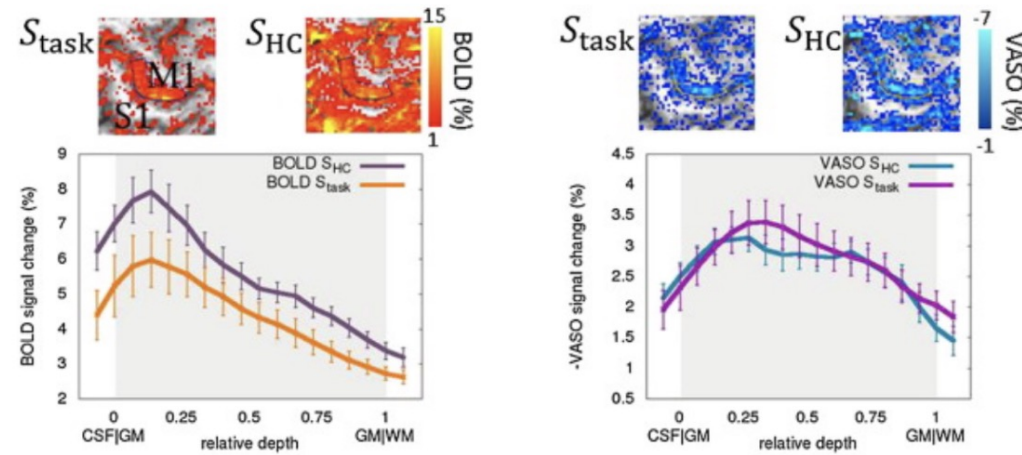
Finger Movement

"Hot Spot" in Cortex

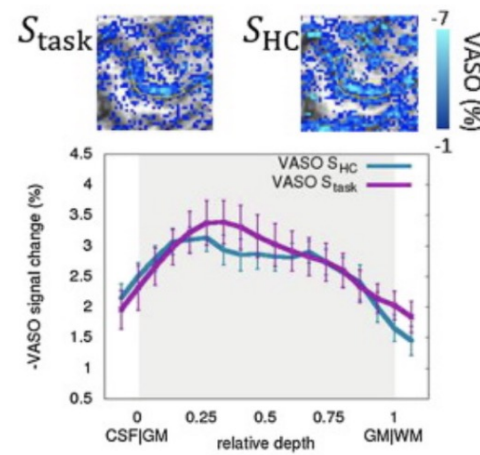


Finger Movement / 5% CO₂

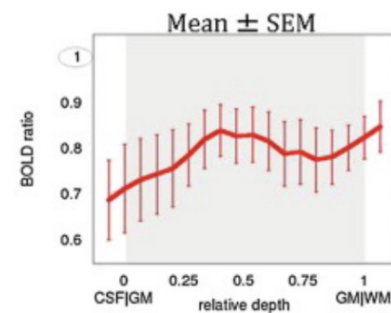
Spatial Localization → calibration (hypercapnia)



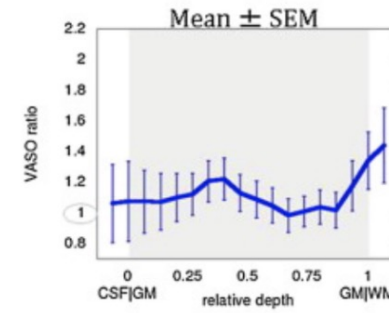
(a)



(b)



(c)



(d)

Challenges

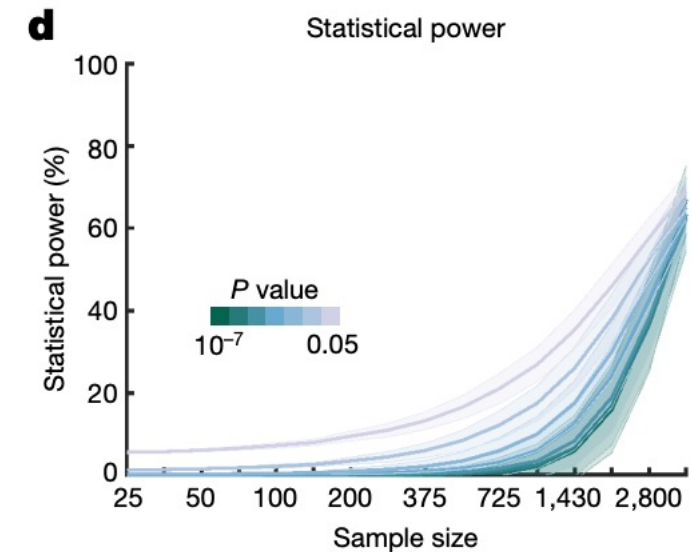
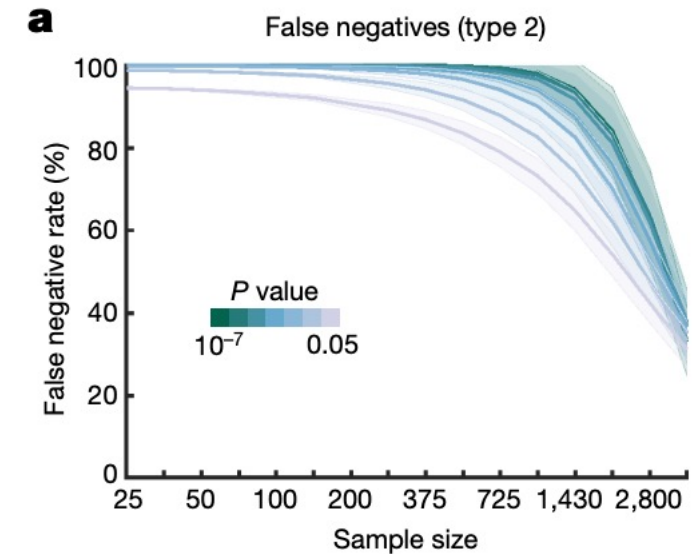
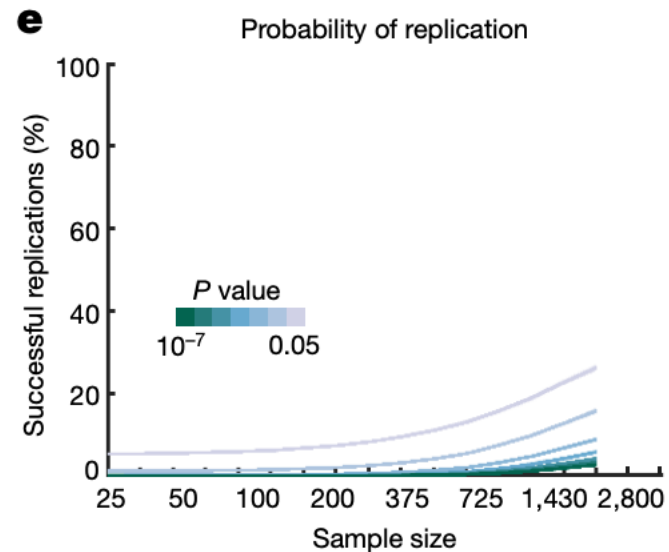
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Reproducible brain-wide association studies require thousands of individuals

[Scott Marek](#) , [Brenden Tervo-Clemmens](#) , [Finnegan J. Calabro](#), [David F. Montez](#), [Benjamin P. Kay](#), [Alexander S. Hatoum](#), [Meghan Rose Donohue](#), [William Foran](#), [Ryland L. Miller](#), [Timothy J. Hendrickson](#), [Stephen M. Malone](#), [Sridhar Kandala](#), [Eric Feczko](#), [Oscar Miranda-Dominguez](#), [Alice M. Graham](#), [Eric A. Earl](#), [Anders J. Perrone](#), [Michaela Cordova](#), [Olivia Doyle](#), [Lucille A. Moore](#), [Gregory M. Conan](#), [Johnny Uriarte](#), [Kathy Snider](#), [Benjamin J. Lynch](#), ... [Nico U. F. Dosenbach](#)  [+ Show authors](#)

[Nature](#) **603**, 654–660 (2022) | [Cite this article](#)



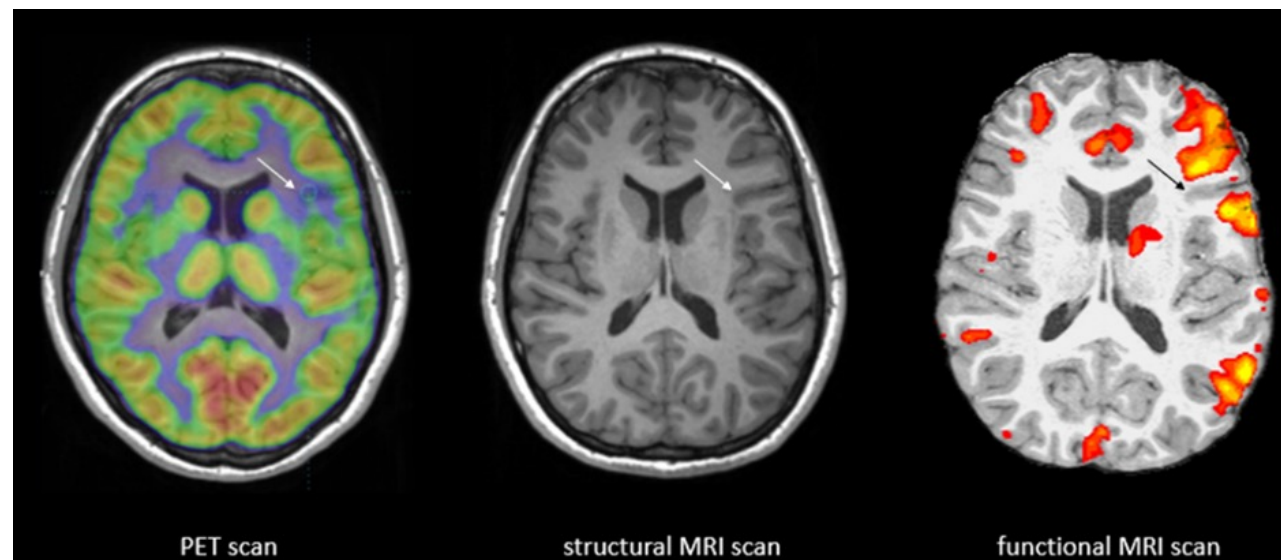
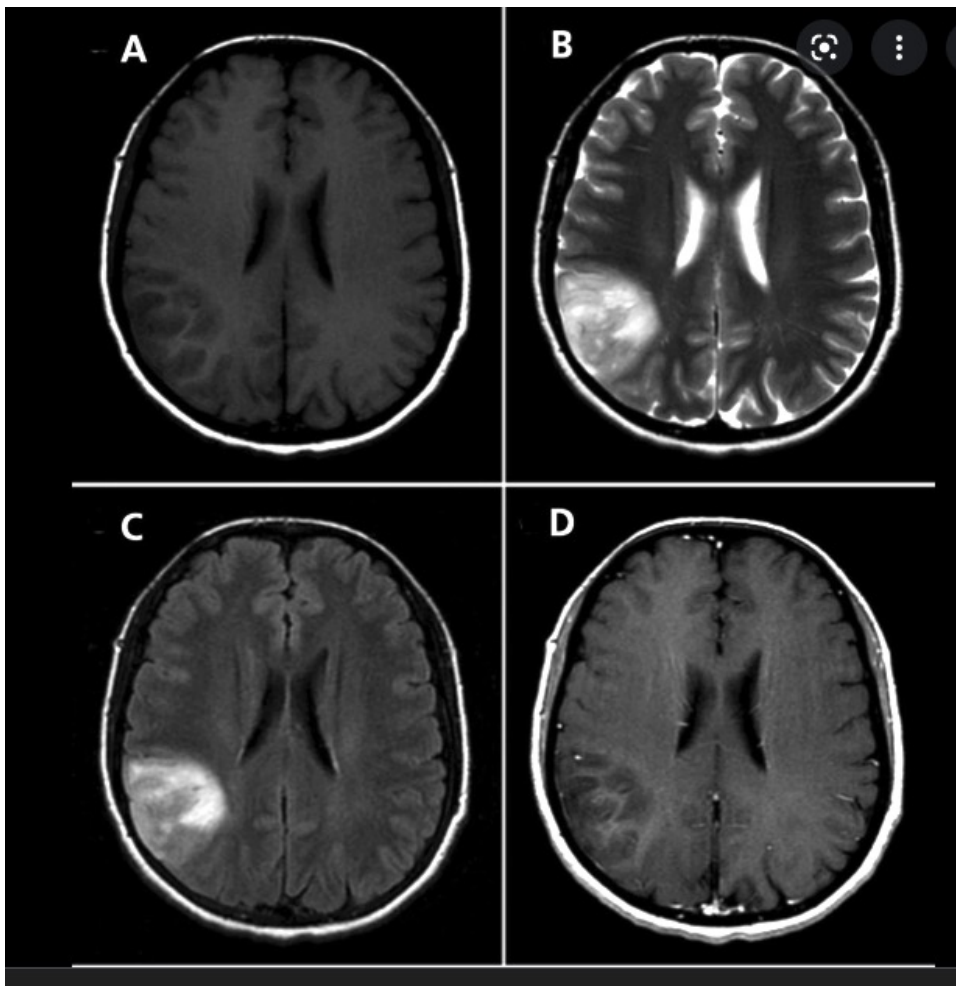
Ways of Improving this....

- More homogeneous populations
- Naturalistic stimuli rather than resting state
- Targeted tasks
- More precise normalization and registration methods
- Multi-variate assessment
- Other measures: dynamics, shapes...

Challenges

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Practical clinical pipeline for fMRI??



Single metric

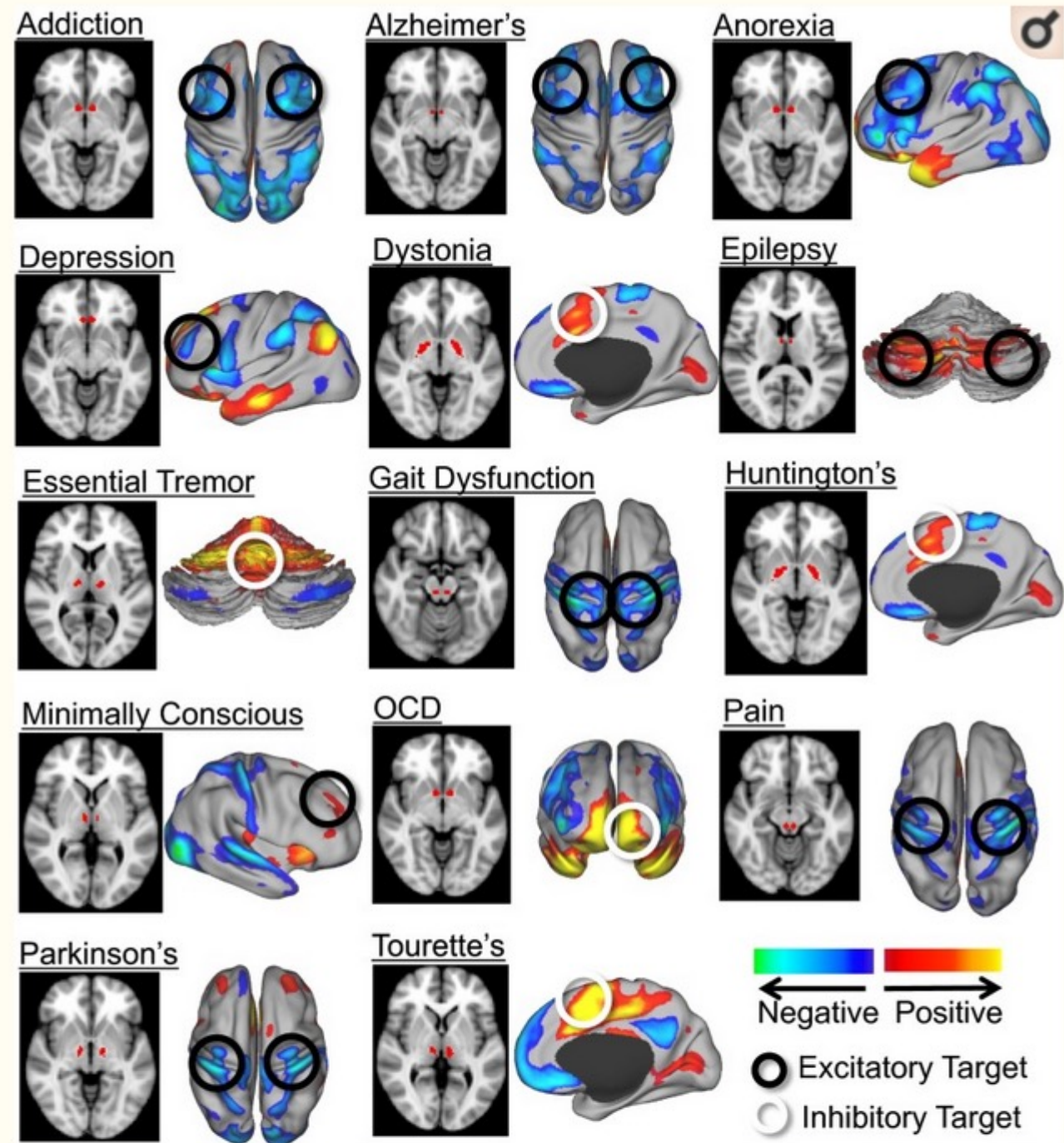
Single contrast weighting

*Hundreds of different ways of making this
Many steps, each which may change results*

Reproducible
Robust to motion
Standard, simple, approved
Updatable
Easily disseminated

Very Hard!

Using fMRI Resting State Connectivity to guide localization of Transcranial Magnetic Stimulation (TMS)

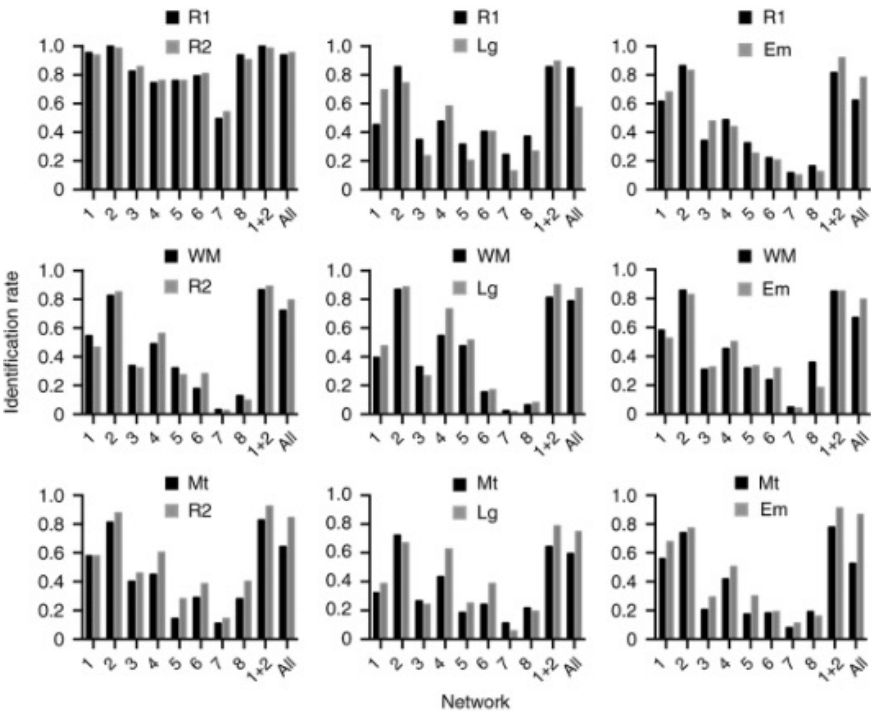


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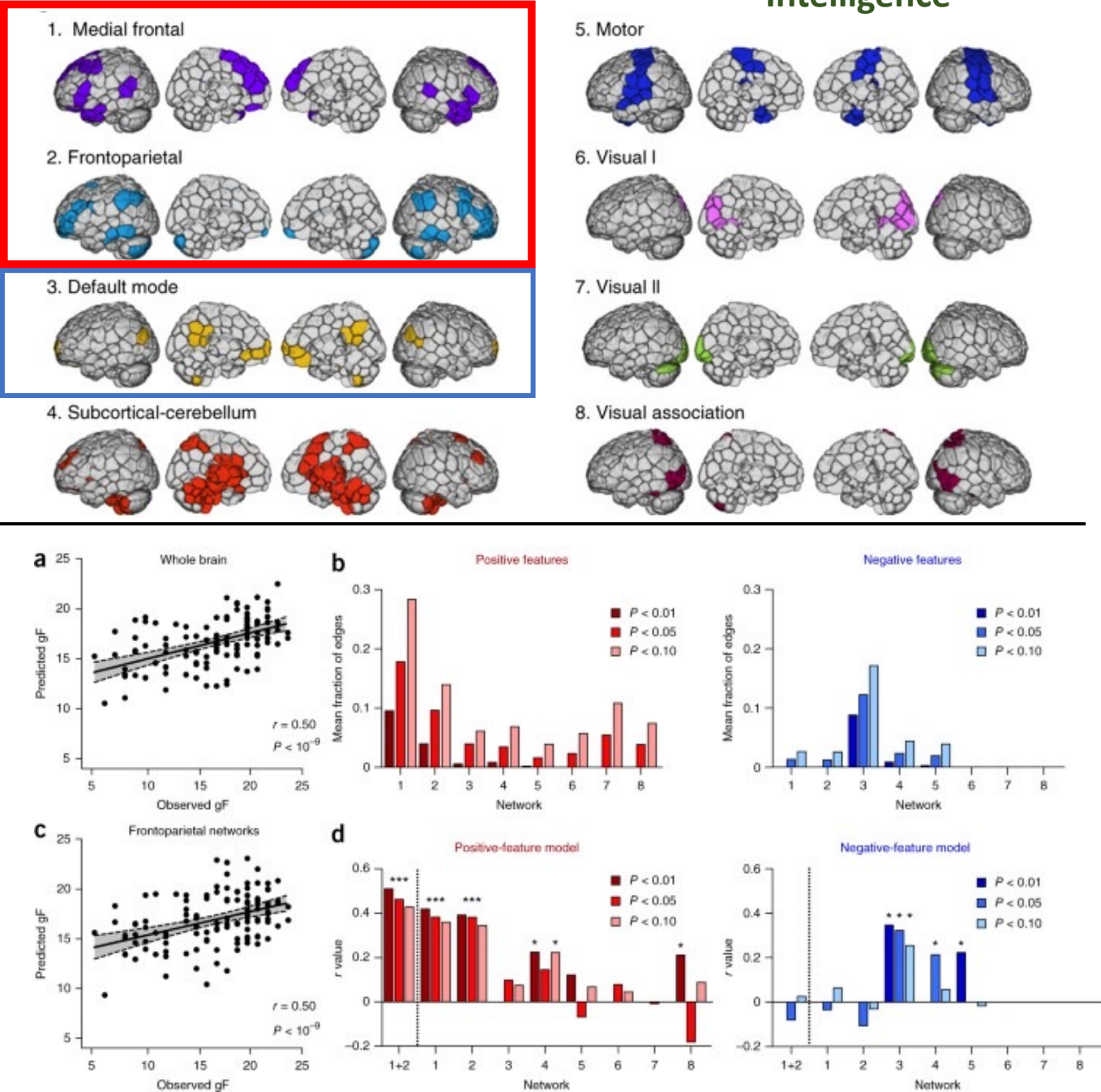
Connectivity strength is unique to individuals and indicative of intelligence

Identification



Finn et al, Nature Neuroscience, 2015

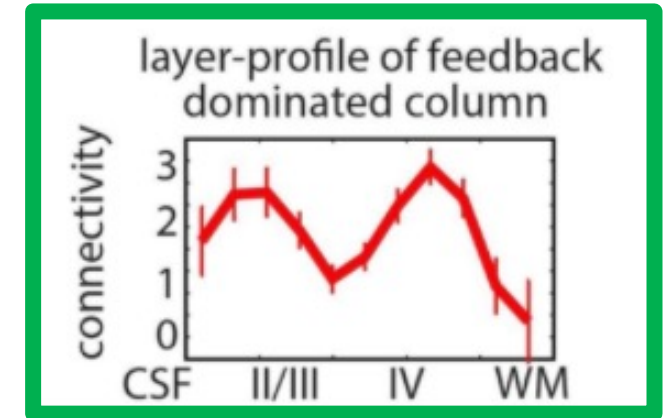
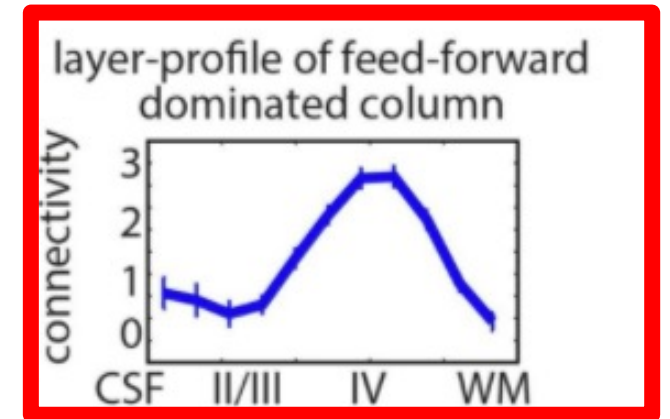
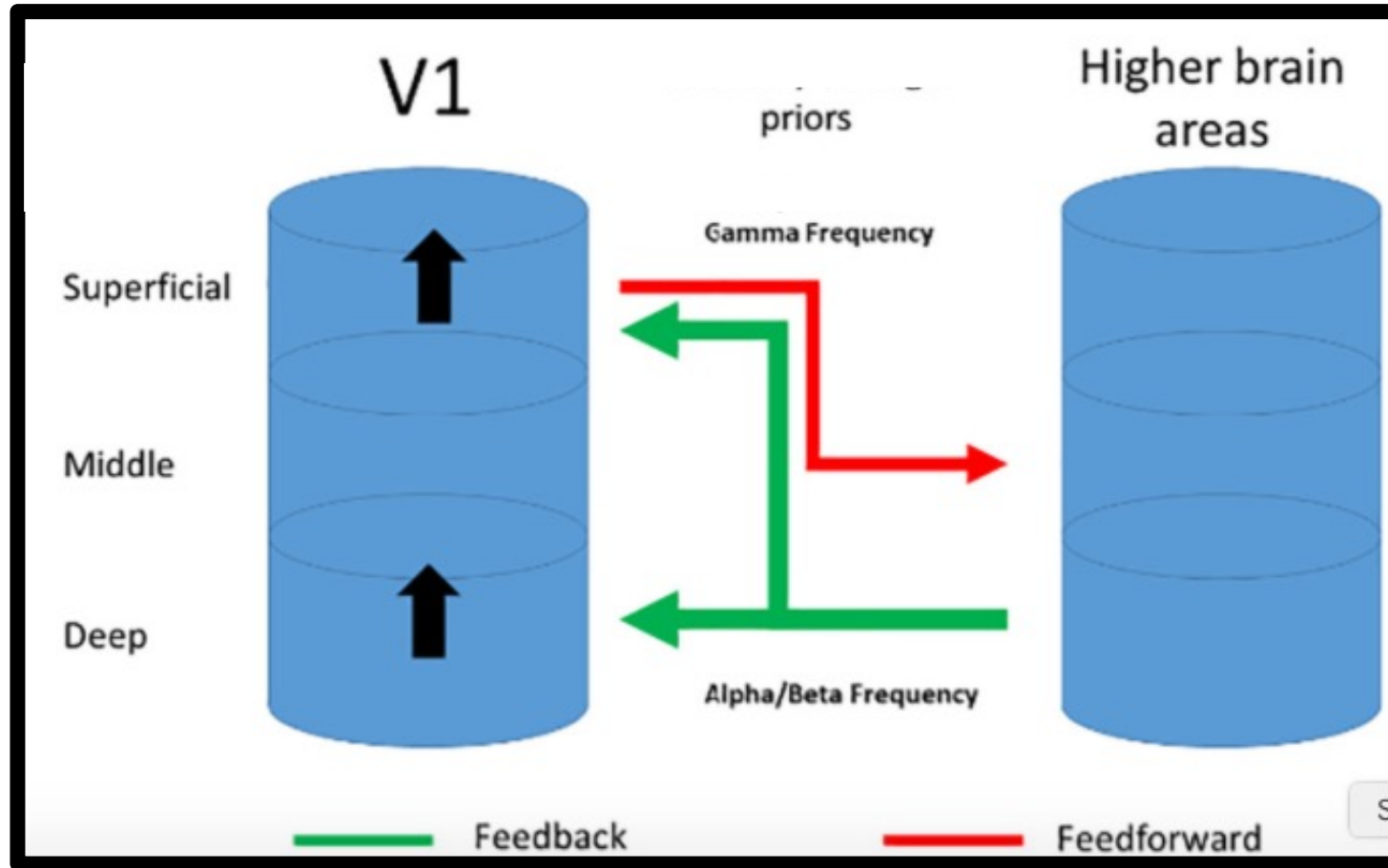
Intelligence



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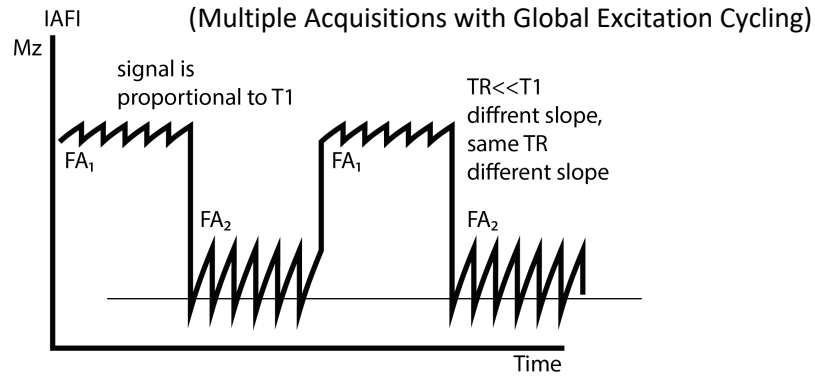
- Models of the world are compared with evidence and at the layer level.
- Layers embody the nodes in the relevant circuitry.
- May provide *directionality* information based on layer *location*.



J. Haarsma et al, The promise of layer-specific neuroimaging for testing predictive coding theories in psychosis, Schizophrenia Research, 2020

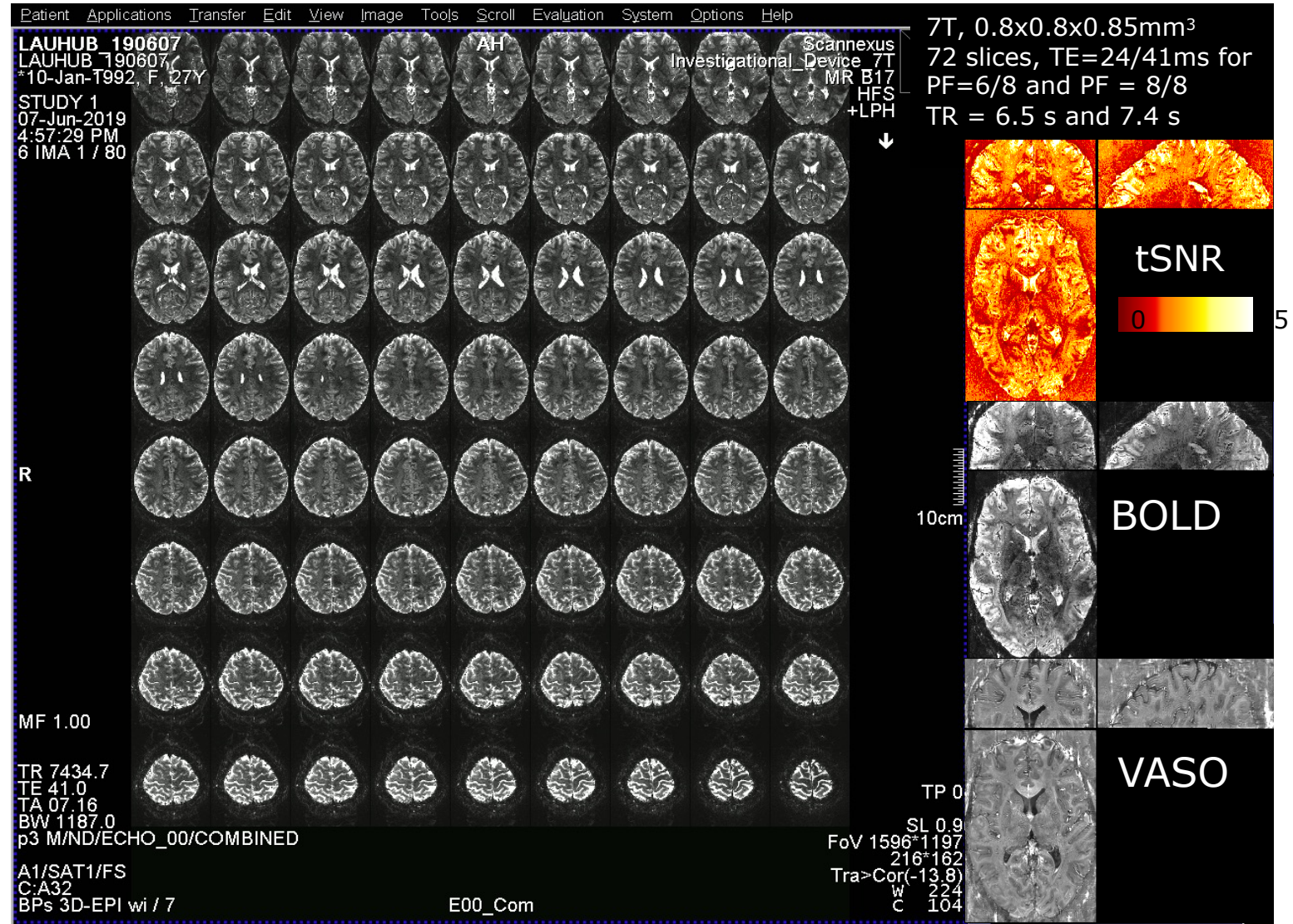
Whole brain layer-fMRI with VASO

MAGEC VASO, T1 weighting between segments



Huber L, Finn ES, Chai Y, Goebel R, Stirnberg R, Stöcker T, Marrett S, Uludag K, Kim SG, Han SH, et al.: **Layer-dependent functional connectivity methods**. *Prog Neurobiol* 2020, doi:10.1016.

Chai Y, Li L, Huber L, Poser BA, Bandettini PA: **Integrated VASO and perfusion contrast: A new tool for laminar functional MRI**. *Neuroimage* 2020, 207:116358.



NIH data: 5 runs of movie watching MAGEC-SS-SI-VASO
selected networks from HCP with GLM

VASO z-scores

Background is MEAN VASO

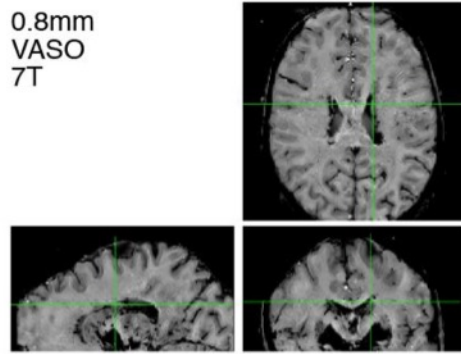
'old' MAGENTOM 7T, NIH
0.8 mm isotropic
104 slices (8 removed)

Connectivity Matrix Approach

extracting layer-dependent whole brain connectomics

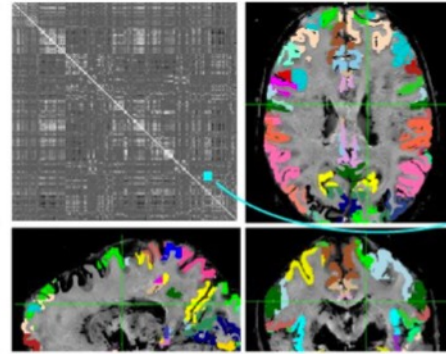
A) VASO whole brain EPI

0.8mm
VASO
7T



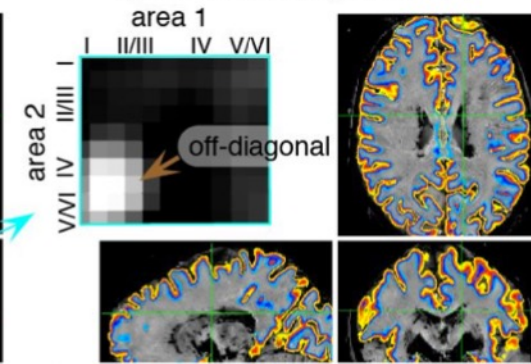
The time series mean image has sufficient anato-mical contrast to-noise-ratio for segmentaion in EPI.

B) atlas of brain areas



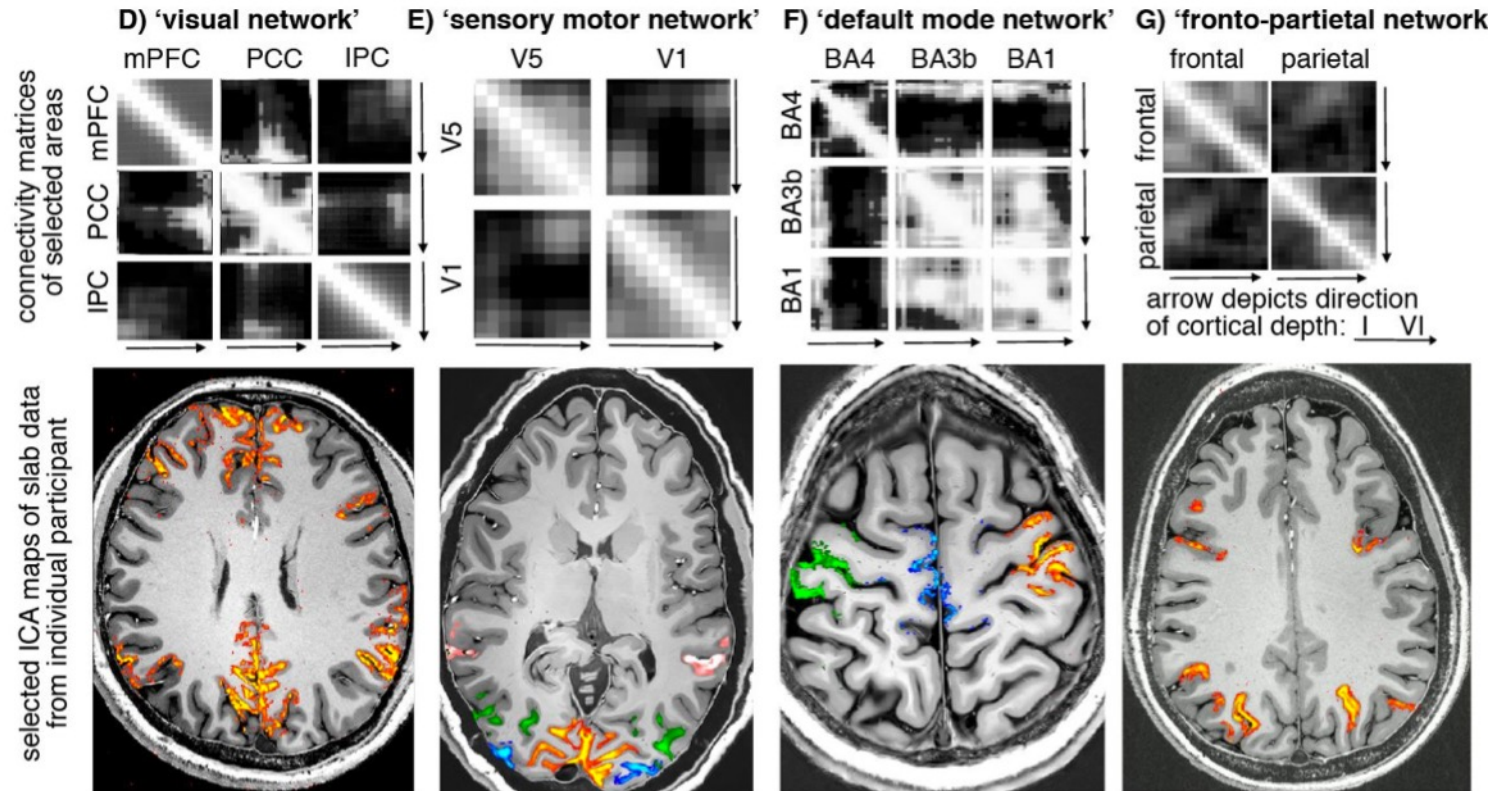
The brain is separated into the common parcels to extract an area-to-area correlation matrix.

C) whole brain layers in EPI



Upon layerification, each edge represents an additional layer-to-layer connectivity matrix. One edge is selected (cyan).

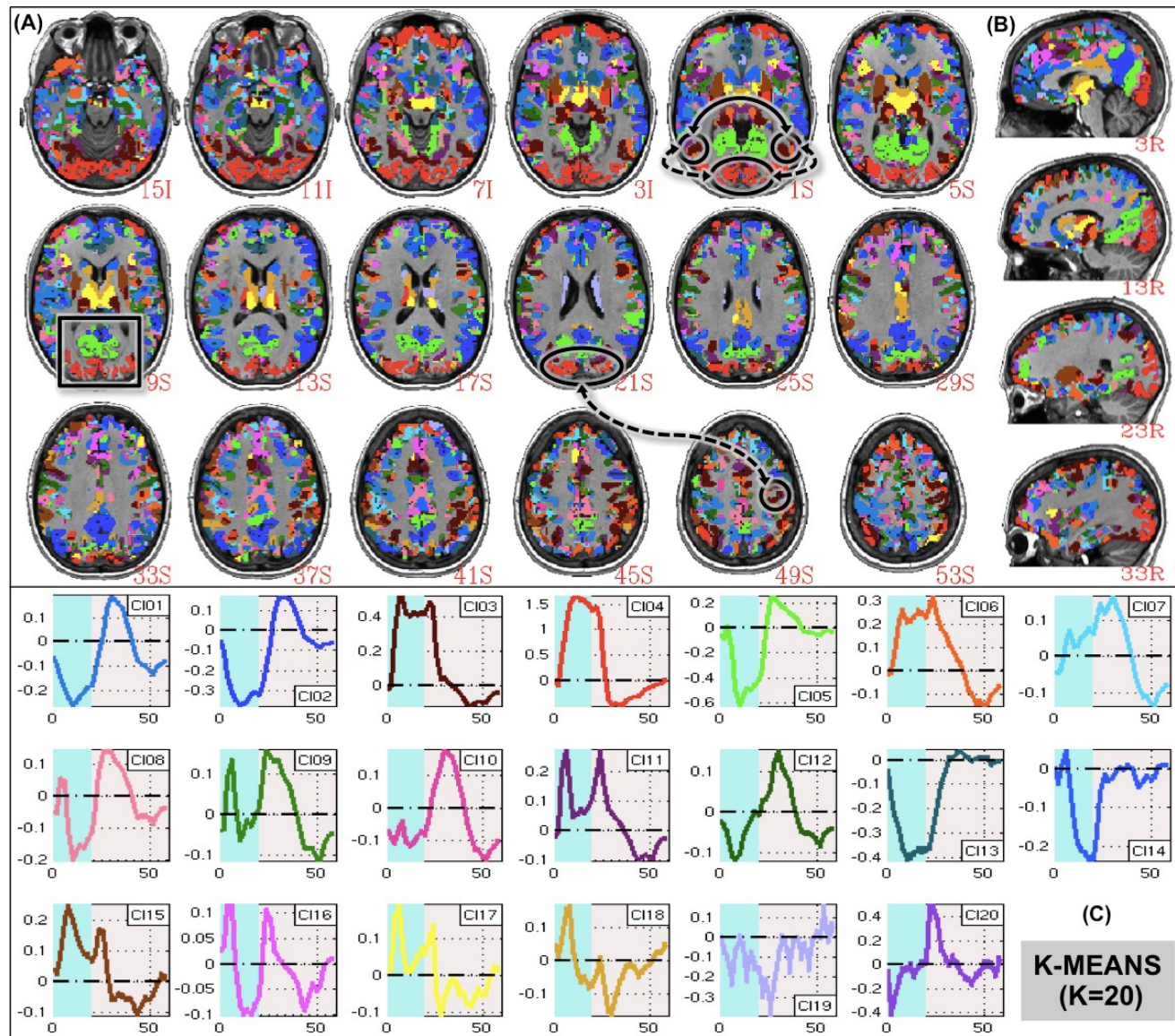
functional layer-connectomes in representative cortical networks



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Deep Sampling of Individual Subjects



9 hours of averaging layer fMRI data
with single subject and simple task

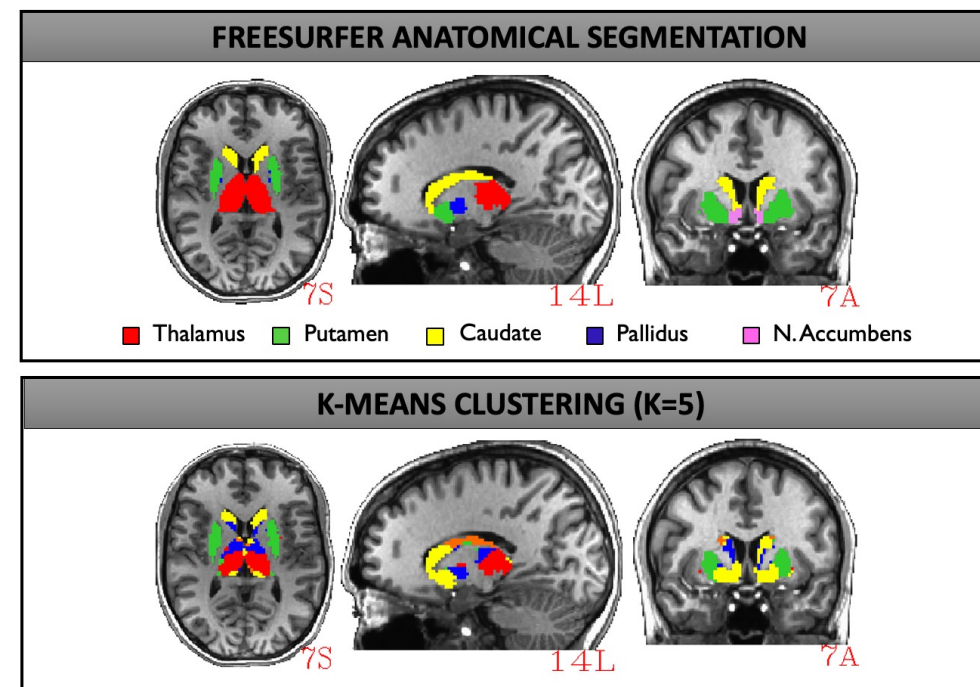
K-means clustering of all time-locked signal

Simple full field checkerboard with
word/letter discrimination task



Subcortical activation

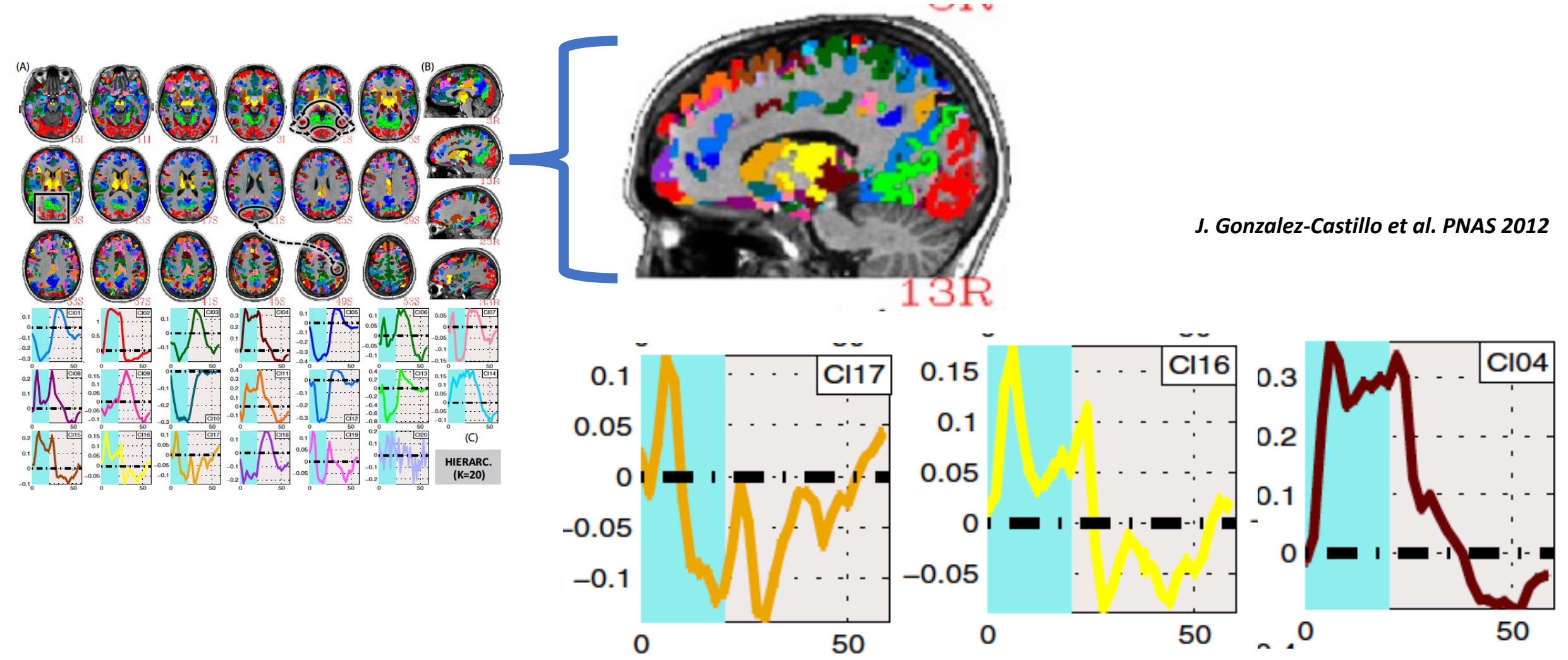
Javier Gonzalez-Castillo



Robust subcortical activity/connectivity assessment.

Many (most?) psychiatric pathologies likely involve disrupted subcortical circuitry.

We need to be able to see this robustly.



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Simultaneous or interleaved contrasts...

- Different BOLD weightings (TE)
- Spin-echo and Gradient-echo...and asymmetric spin-echo.
- Perfusion, Blood Volume, BOLD
- w/ and w/o Diffusion weighting (removal of intravascular blood)
- w/ and w/o Inflow nulling
- Different flip angles
- w/ and w/o Magnetization transfer contrast.

Exploring the Potential for other MR Contrasts at 7T Related to Mental Health

- **Glymphatic system: Perivascular space, CSF dynamics**

Alzheimer's disease, Depression

(Multi-echo ASL, ultra-fast T1-weighted imaging, phase contrast)

- **Global brain inflammation**

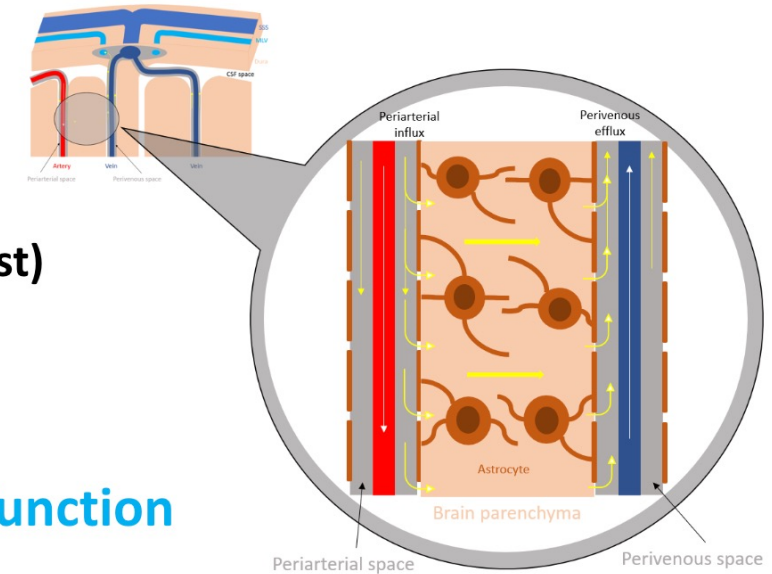
Alzheimer's disease, Depression, Psychosis

(quantitative T1, T2, diffusion)

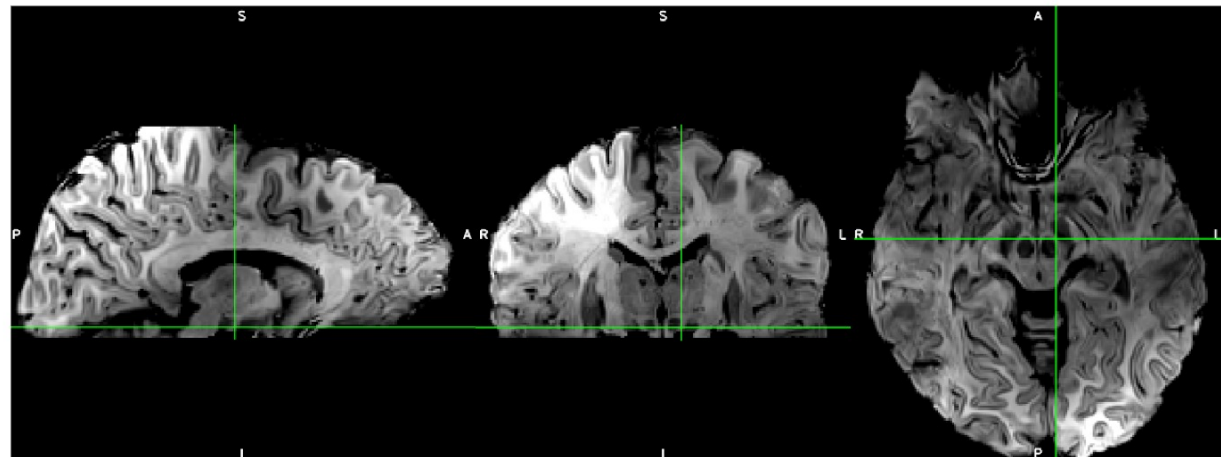
- **Neuromelanin in Substantia Nigra: proxy for dopamine function**

Parkinson's disease, Schizophrenia

(MT-SWI)



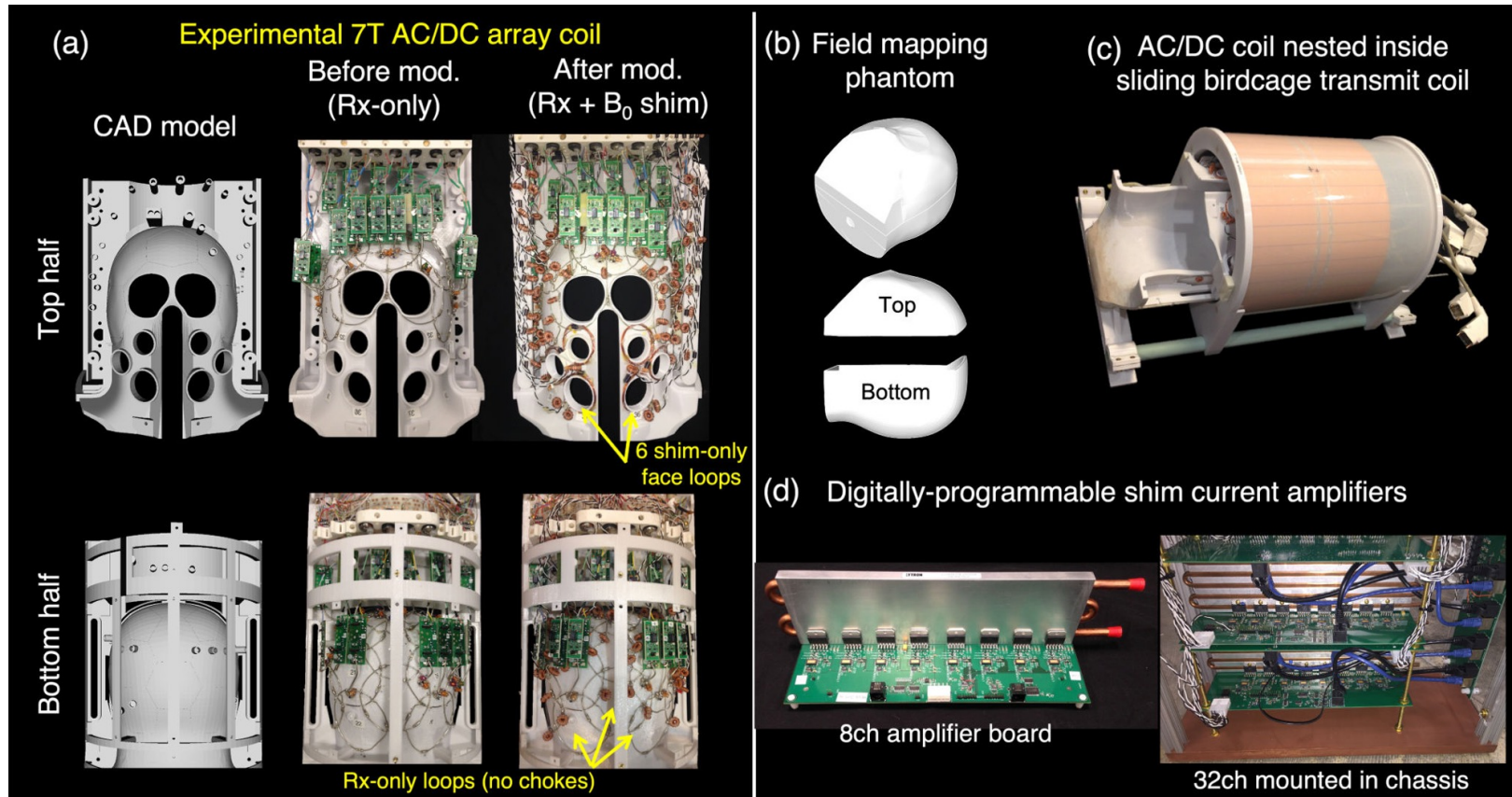
MT-SWI 3D-EPI sequence at 7T
0.8mm x 0.8mm x 0.84mm
(Y. Chai - SFIM)



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AC / DC Coil



Stockmann, J. P.; Arango, ... J. K.; Setsompop, K.; Polimeni, J. R.; Wald, L. L. A 31-Channel Integrated “AC/DC” B_0 Shim and RF Receive Array Coil for Improved 7 Tesla MRI. *Magn Reson Med* **2022**, 87 (2), 1074–1092.
<https://doi.org/10.1002/mrm.29022>.

Controversies

Practices that may be incorrect:

- *Use of global signal regression*
- *Connectivity interpretation*
- *Parcellation templates, assumptions with normalization*
- *Thresholding*
- *Simple regressor models*

Discoveries of shortcomings that get amplified by non-experts:

- *Dead Salmon (false positives)*
- *Double dipping (voodoo correlations)*
- *Clustering Conundrum*
- *Multi-center single data set analysis and findings all over the place.*
- *1000's of subjects (Big Data BWAS Conundrum)*
- *Hemodynamic activation but no electrophysiology signatures*

Findings that are intriguing but have not been widely reproduced

- *Activation-induced changes in:
diffusion, neuronal currents, etc..*
- *Activation-induced BOLD in white matter*
- *Pre-undershoot*
- *Many small N group comparisons*

Mysteries

- Why does the BOLD response (activation -> blood hyperoxygenation) happen?
- What are the neuronal/hemodynamic mechanisms behind BOLD transients, nonlinearities, inhomogeneities?
- Is inhibition vs excitation differentiable?
- What are the sources and types of spontaneous fluctuations and connectivity? What is the global signal?
- What is the purpose of resting state fMRI?
- What are we missing in activation? Simple regressors, low sensitivity, large/fixed parcellations...
- Why is the parcellation size what it is? Are there finer natural parcellations? What is meaningful?
- Do parcellations vary across individuals and time?
- Best way to compare brains across/within groups and across individuals at different resolutions?
- How relevant is the spatial/temporal scale of MRI for deriving principles of cognition?

Challenges

- Seamless data/code pooling and sharing
- Removal of ALL non-neuronal noise & understanding all fluctuations.
- Spatial normalization of BOLD signal weighting variation across brain.
- Real time assessment of ongoing state: fully understanding resting state
- Clinically useful “biomarkers”
- Practical clinical implementation
- Full individual subject characterization (similarities and differences)
- Adaptive parcellation (global hyper alignment?) – accounting for differences.
- Layer fMRI -> whole brain directional connectivity and hierarchy, dealing with massive amounts of data, how to pool and compare data across subjects?
- Multimodal integration (EEG, optical, structural, vascular, fMRI)
- Subcortical fMRI and connectivity.
- Robust subcortical activity/connectivity assessment.
- Temporal/spatial resolution of 10 ms and 0.1 mm. – whole brain.
- More contrasts in the time series.
- Uniform shimming across whole brain.
- Migration from cartography to mechanistic understanding (models..)

Controversies Mysteries Challenges

