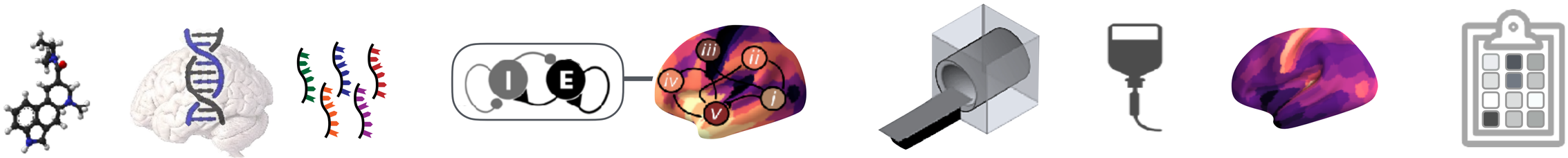
Modeling Connectivity: Biophysical Network Modeling



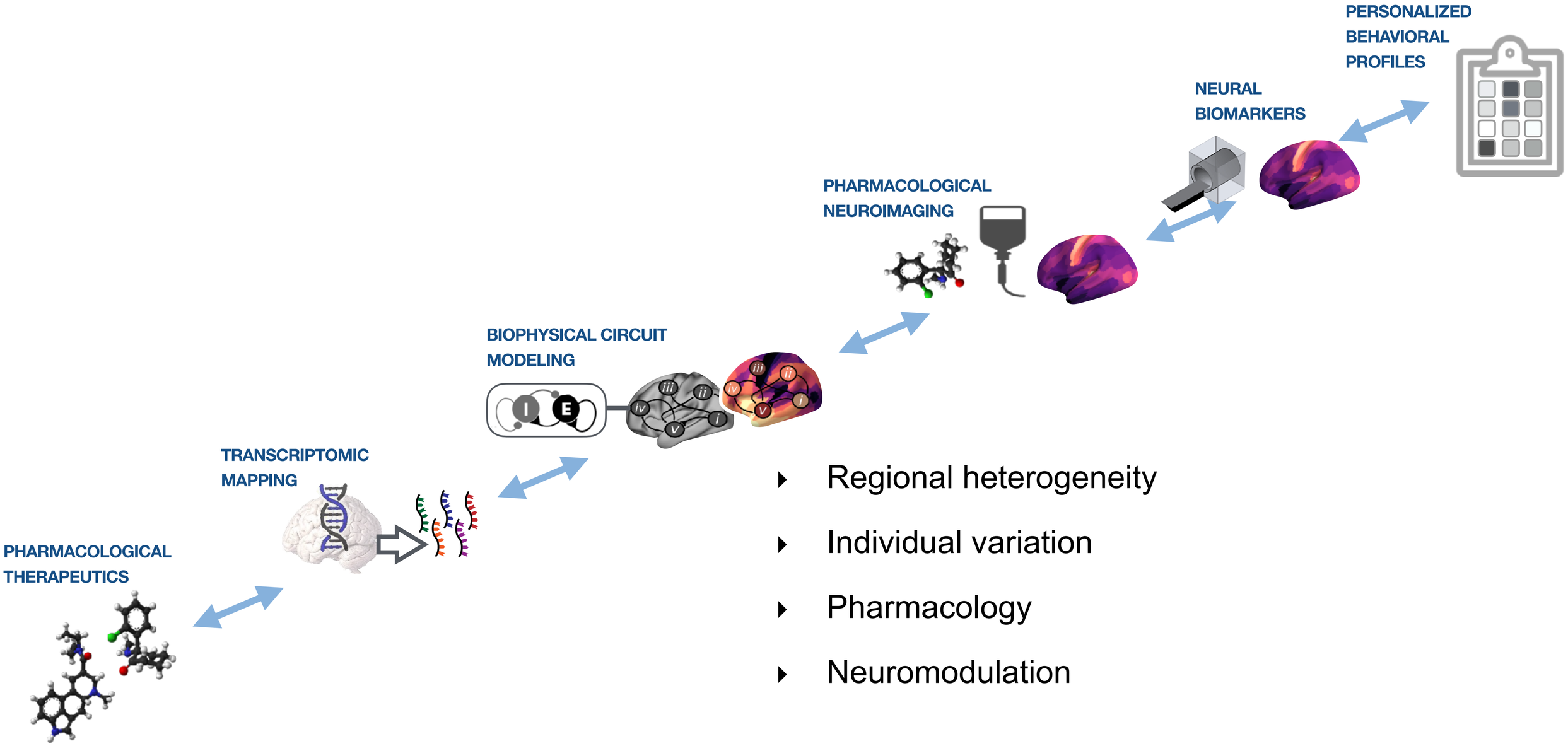
John D. Murray

Division of Neurocognition, Neurocomputation, and Neurogenetics (N3)

Department of Psychiatry

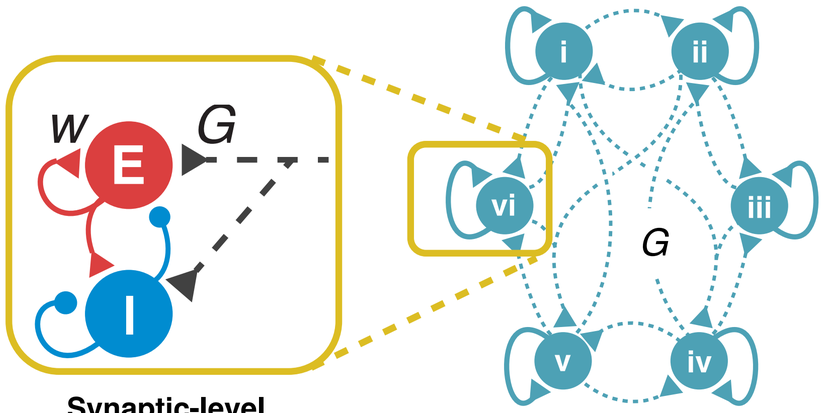
Yale School of Medicine

Computational Psychiatry via bridging levels of analysis with neuroimaging and neural circuit modeling



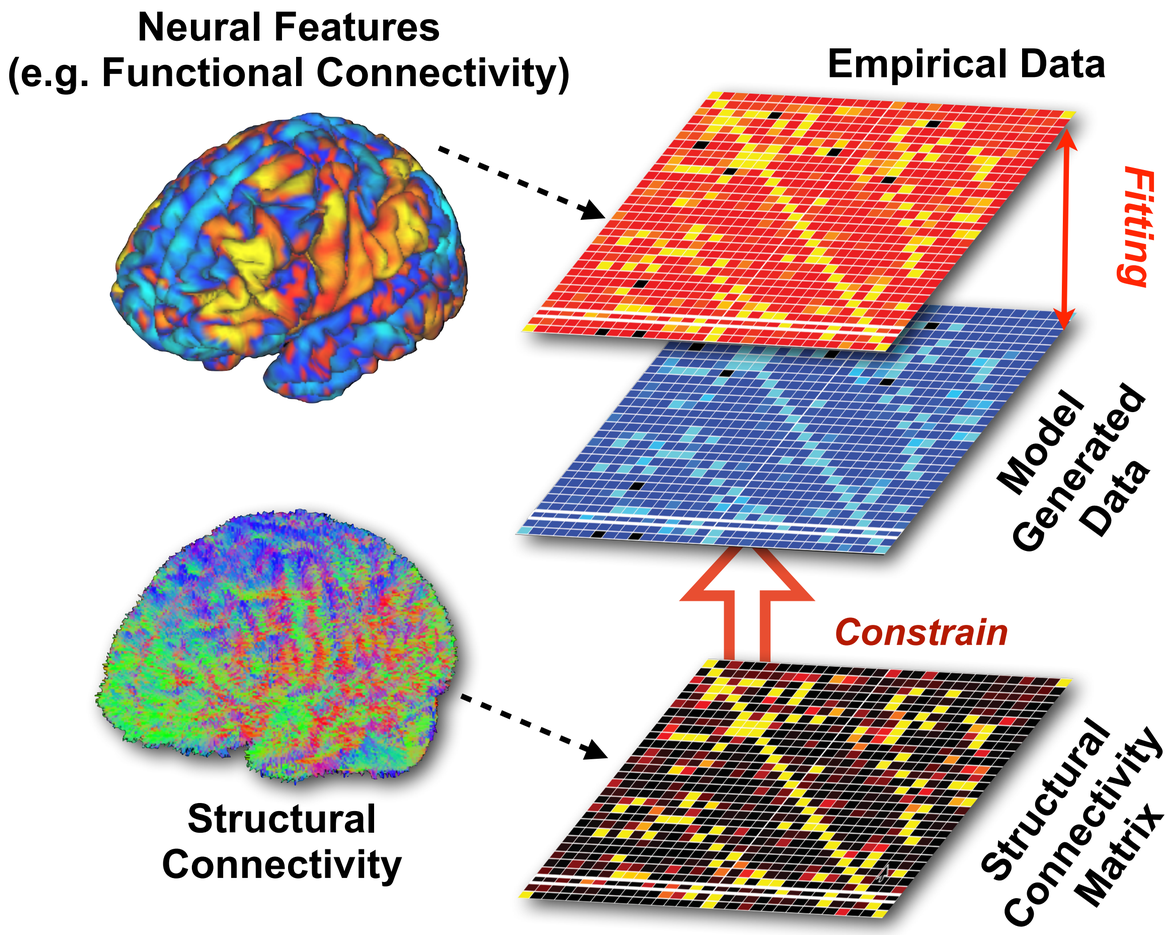
- Regional heterogeneity
- Individual variation
- Pharmacology
- Neuromodulation

Biophysical modeling of large-scale resting-state networks



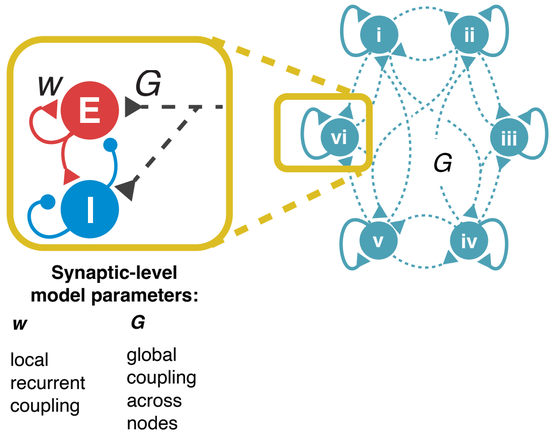
Synaptic-level model parameters:

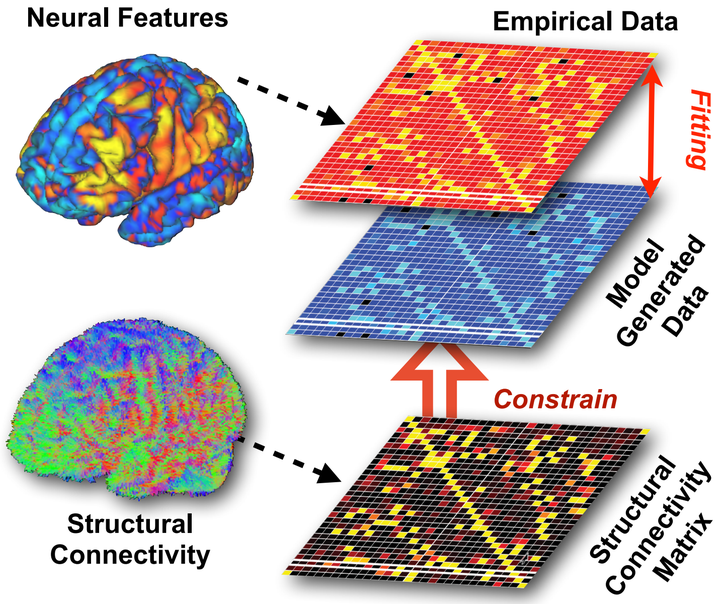
w	***G***
local recurrent coupling	global coupling across nodes



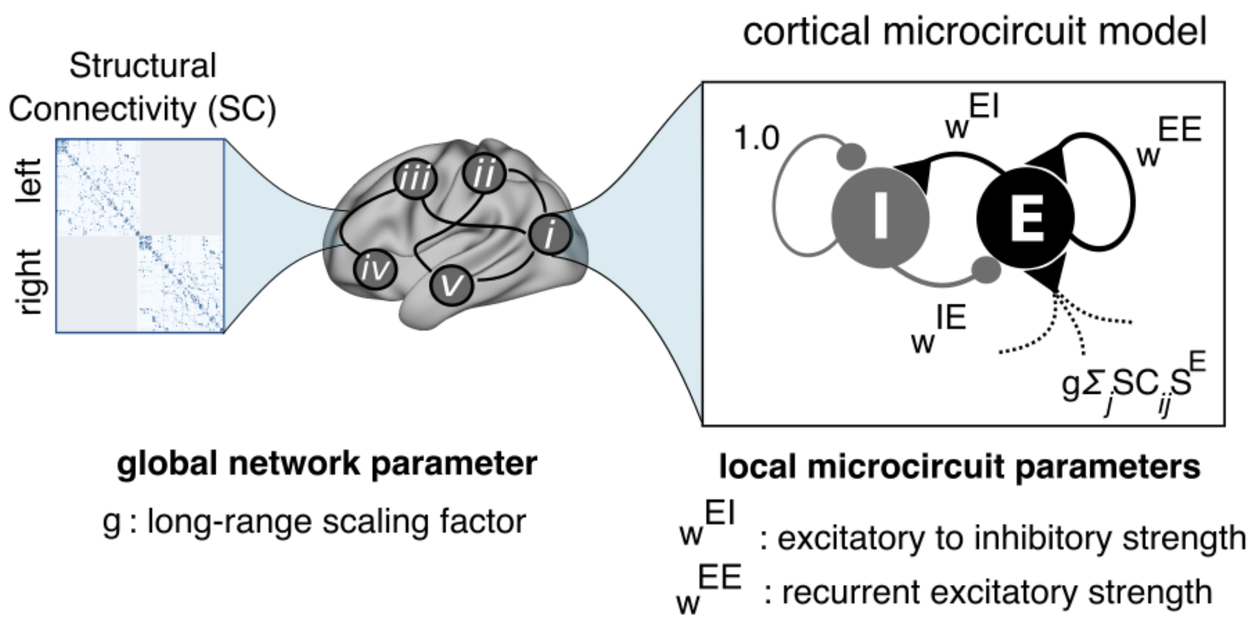
Biophysical modeling of large-scale resting-state networks

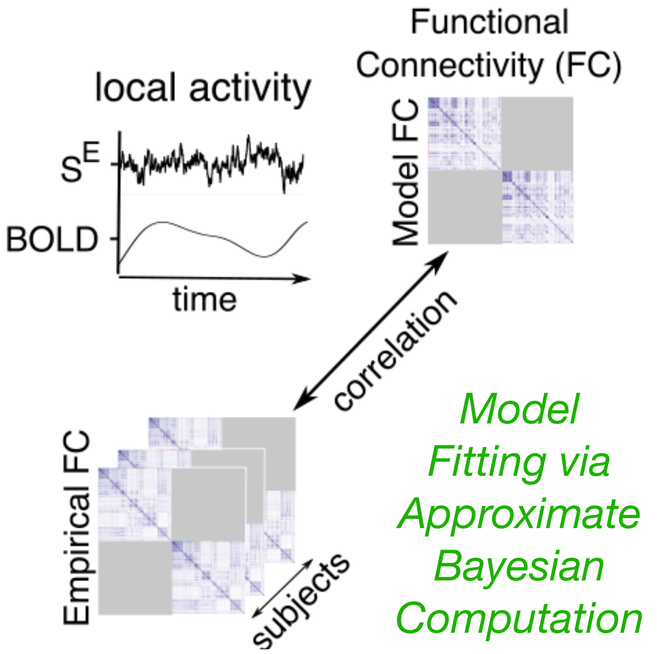
- Need to select local node model
  - Depends on phenomena and parameters of interest
- Typically long-range connectivity pattern is fixed
  - Fewer fit parameters, goal is not to get a great fit to data
- Key aspect of models is that parameters are neurobiologically interpretable
- Examples of types of questions one can pursue:
  - How does variation in local circuit properties across brain areas produce interesting features of empirical data?
  - How does a hypothesized synaptic-level perturbation produce systems-level effects observed in empirical data?



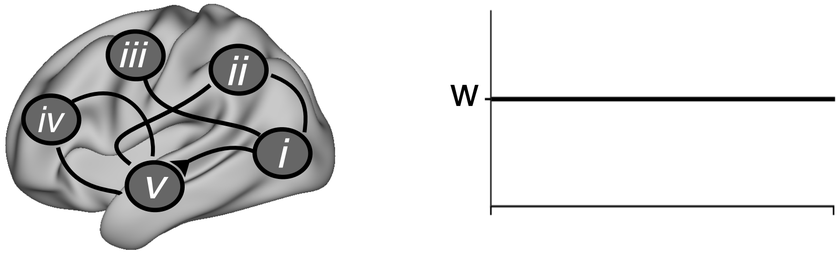


Model with heterogeneous local circuit properties

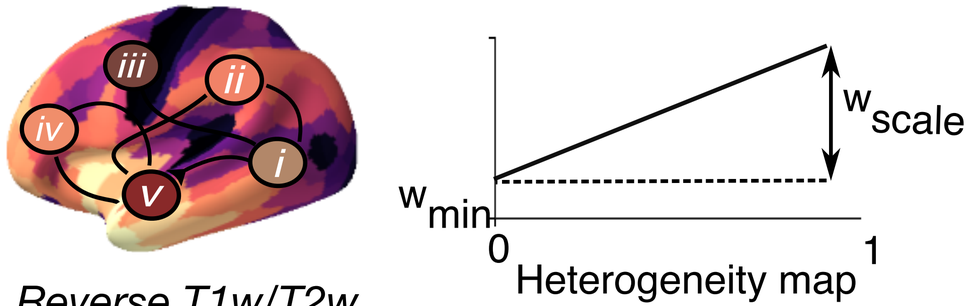




Homogeneous model



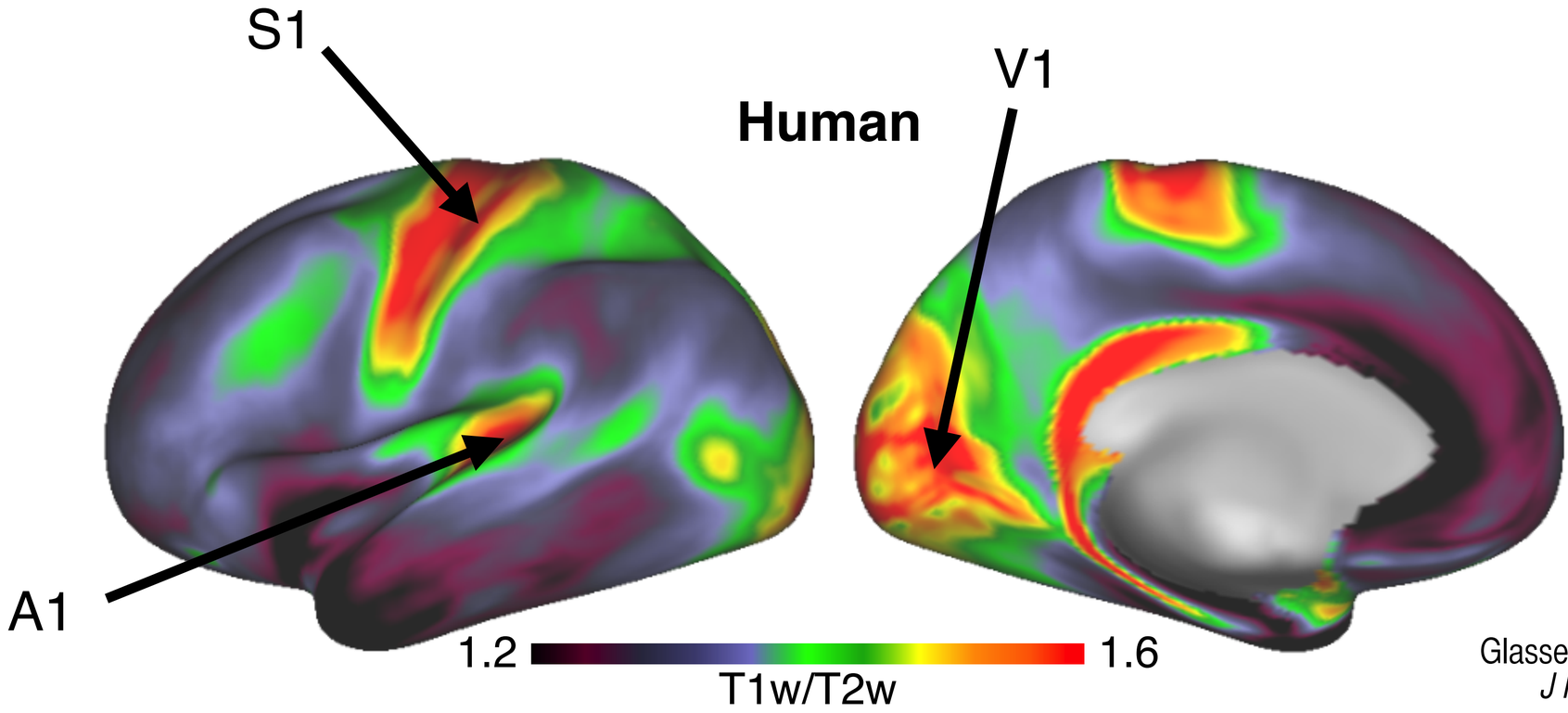
Heterogeneous model



Reverse T1w/T2w myelin map

Demirtas M, et al. (2019) *Neuron*

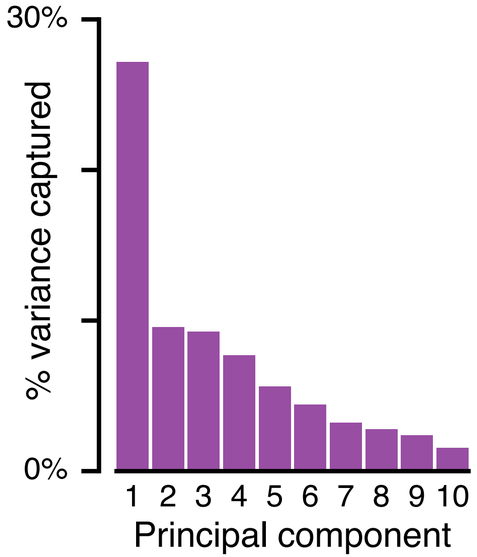
Cortical T1w/T2w map as a proxy measure for cortical hierarchy

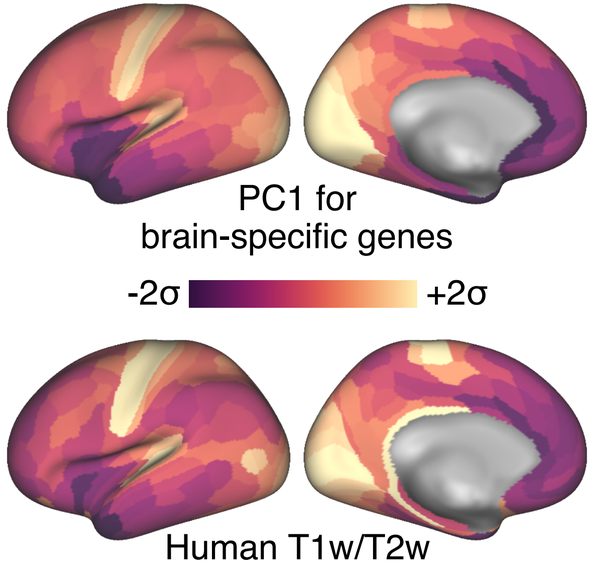


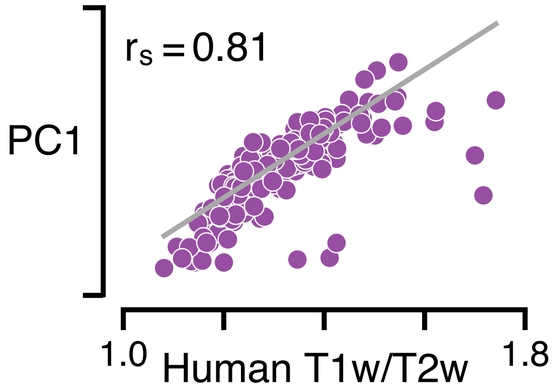
Glasser et al. (2011)
J Neurosci

Burt et al. (2018) *Nature Neurosci*

T1w/T2w topography captures the dominant axis of transcriptional variation across human cortex







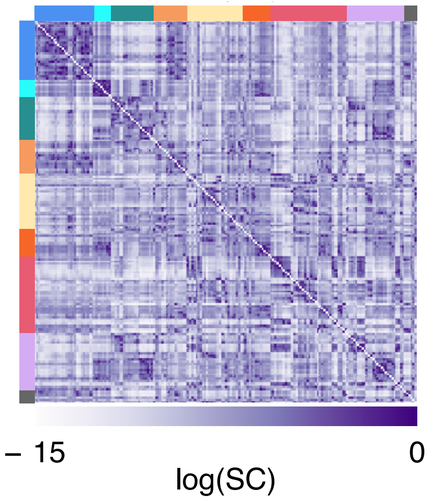
- Cortical gene expression variation is dominated by a single principal axis which is highly correlated with the T1w/T2w map
- Hierarchical gradients of microscale properties may contribute to sensory–association specialization of cortical function.

Burt et al. (2018) *Nature Neurosci*

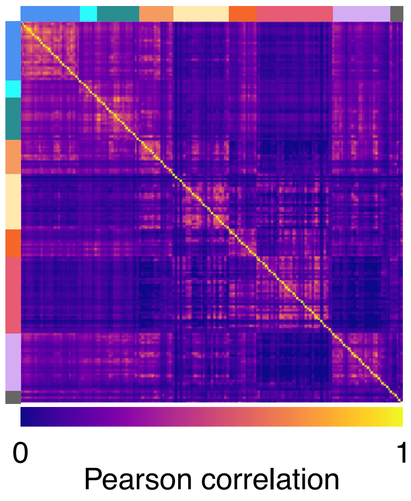
Murat Demirtaş

Simulated functional connectivity in large-scale models

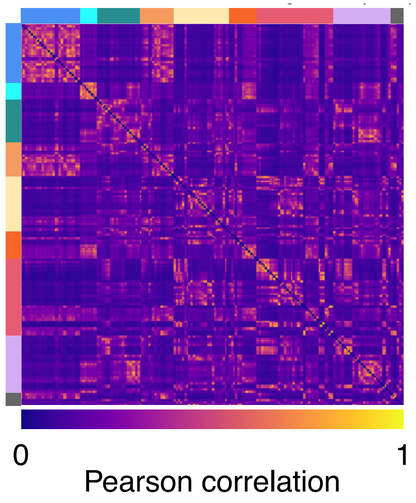
Empirical structural connectivity (SC)



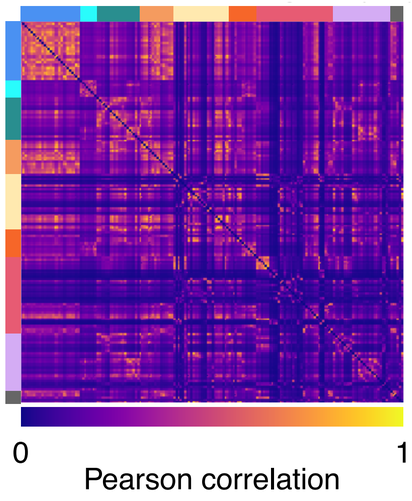
Empirical functional connectivity (FC)



Homogeneous model FC

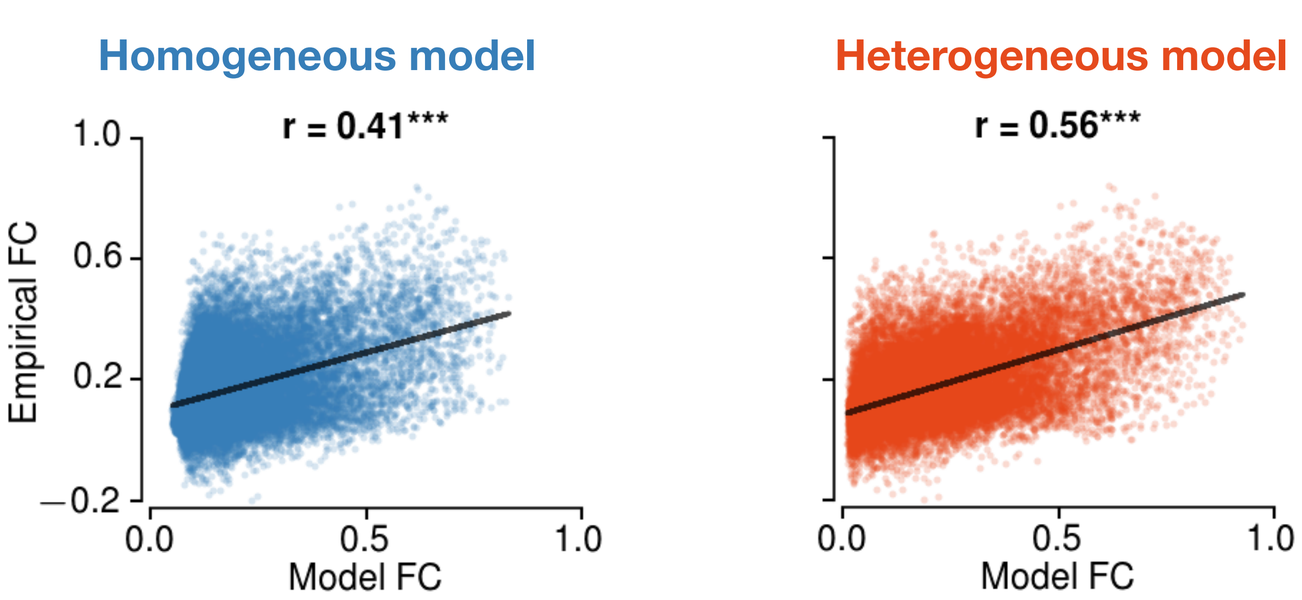


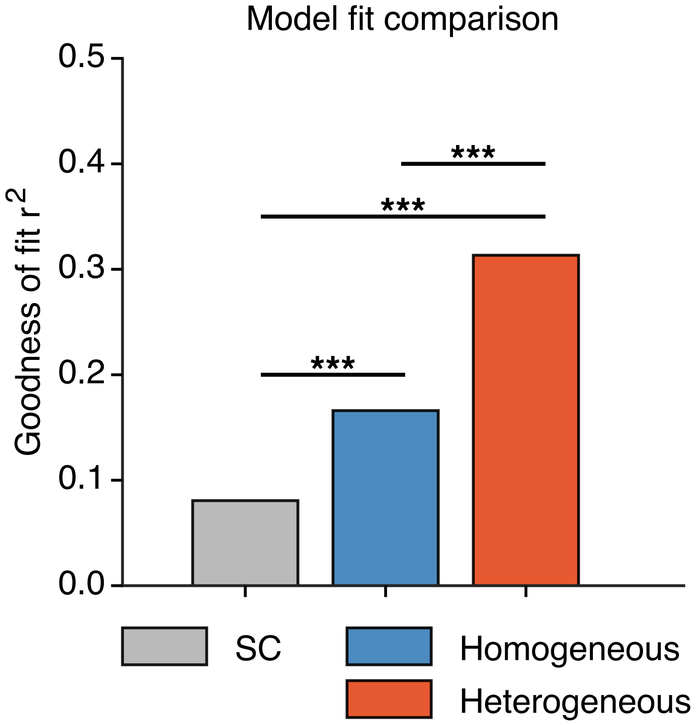
Heterogeneous model FC

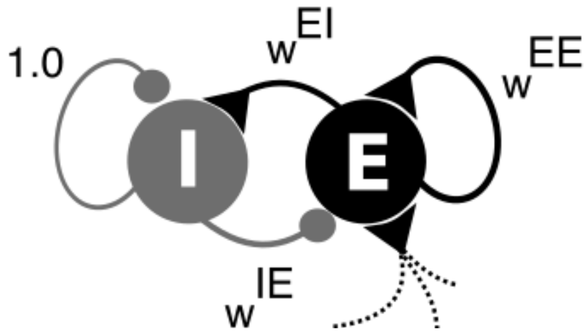


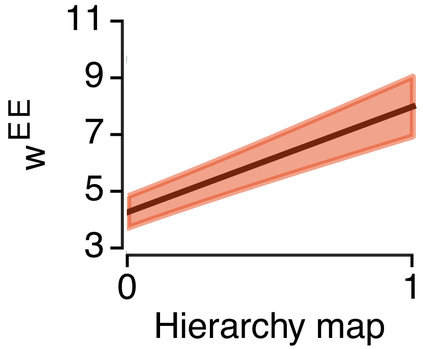
Demirtas M, et al. (2019) *Neuron*

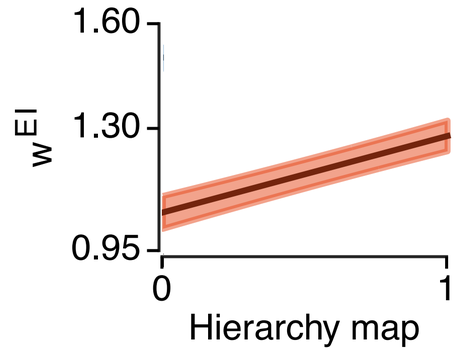
Hierarchical heterogeneity improves model fit to functional connectivity









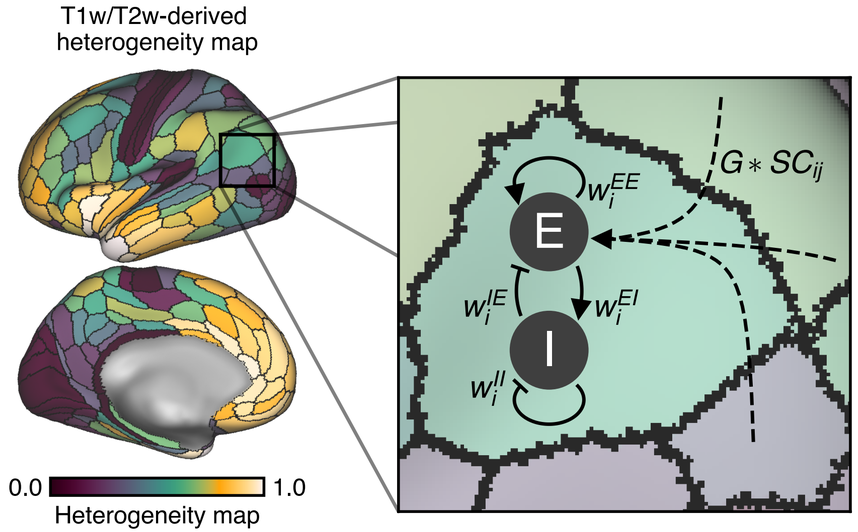


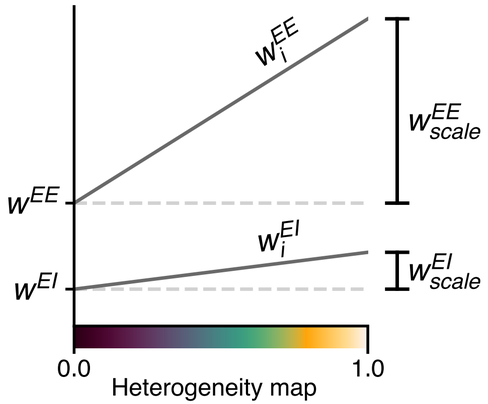
Increasing local recurrent strength along cortical hierarchy

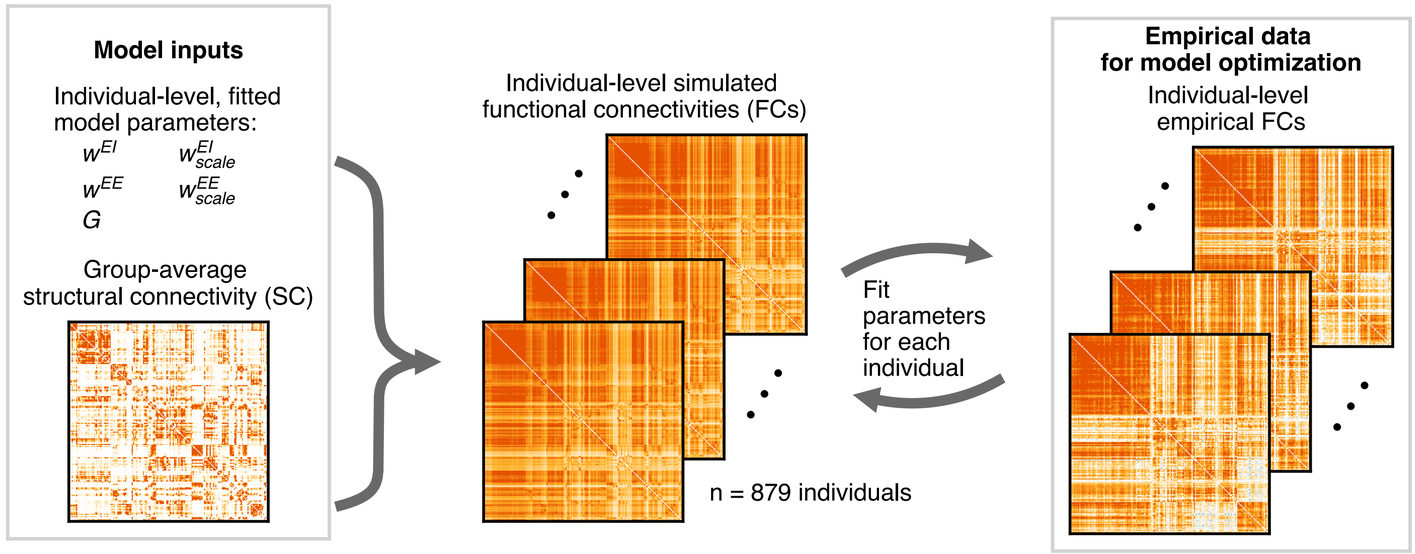
Demirtas M, et al. (2019) *Neuron*

Rachel Cooper

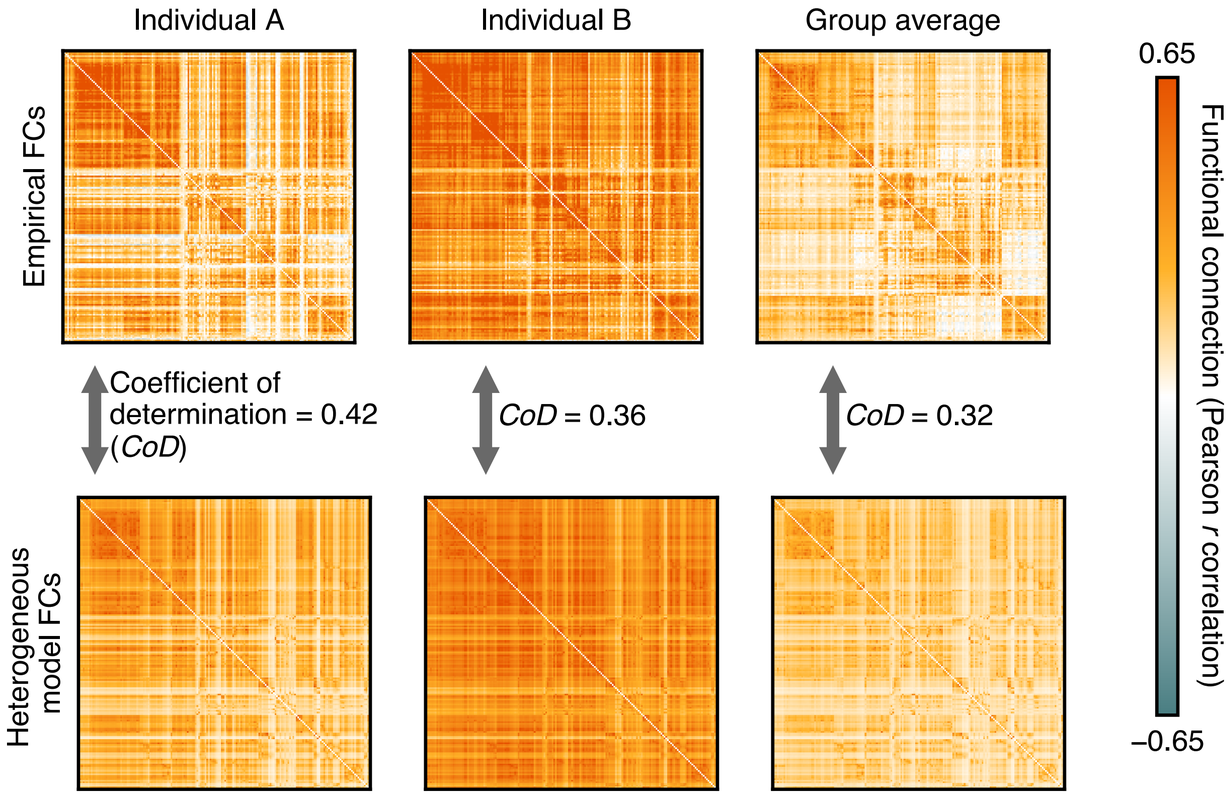
Individual-subject modeling of functional connectivity

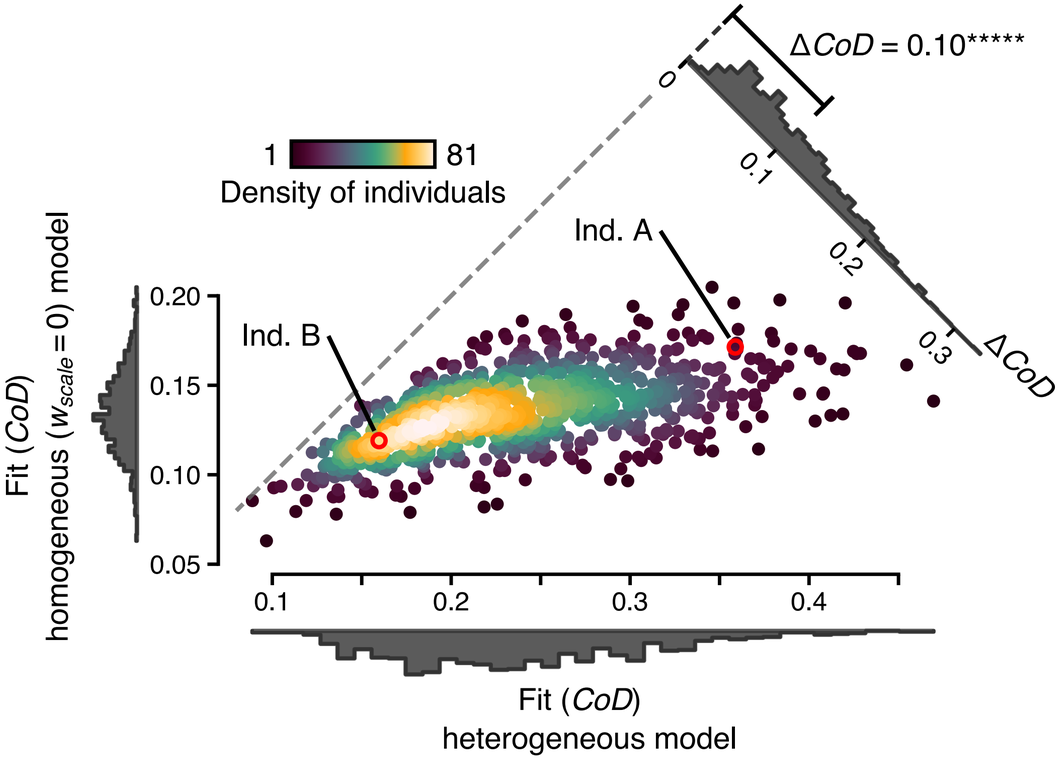






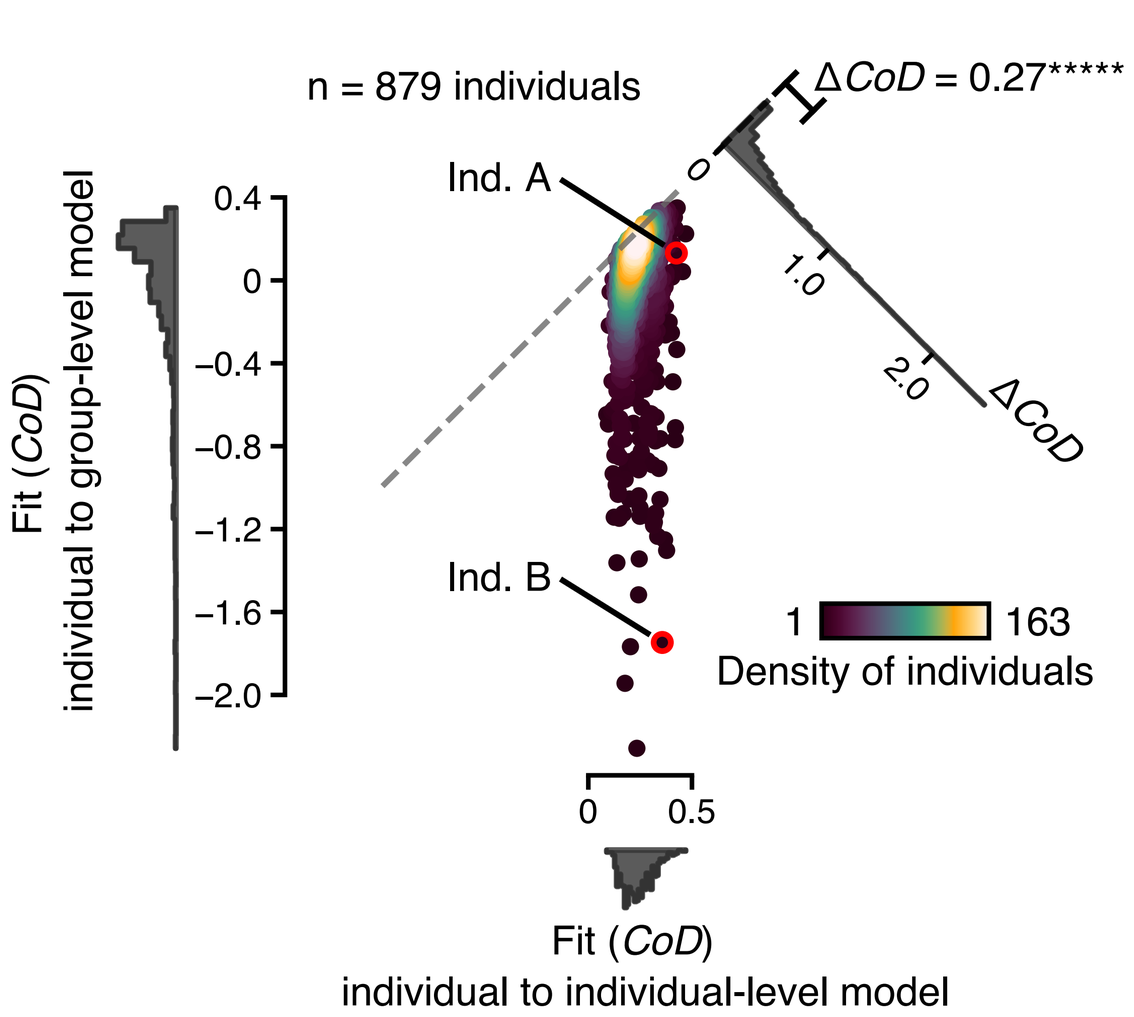
Individual-subject modeling of functional connectivity

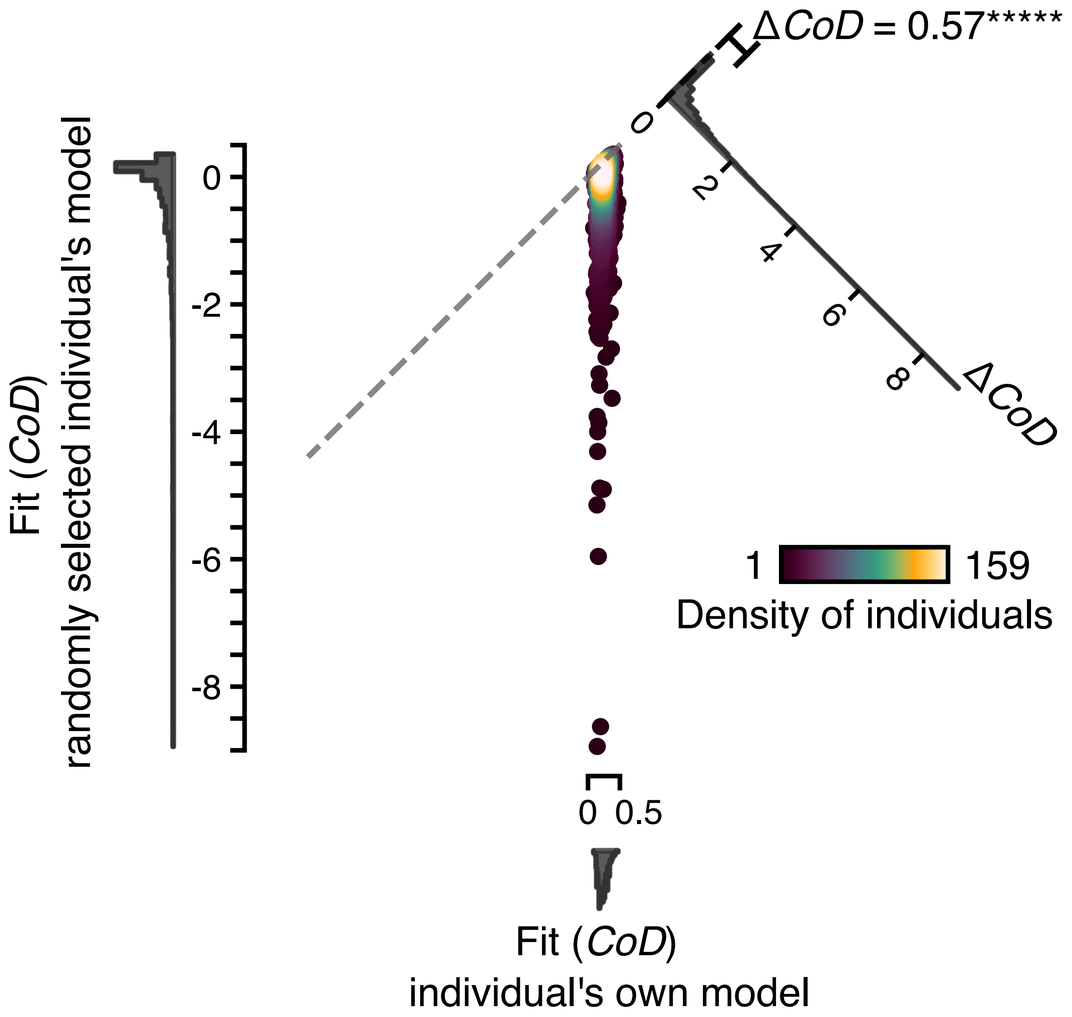




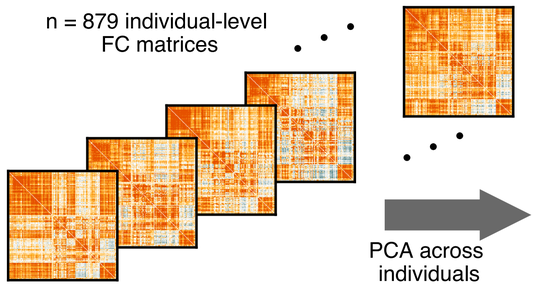
Fit measure: $$\text{Coefficient of Determination (COD)} = 1 - \frac{\text{MSE(predicted, observed)}}{\text{MSE(predicted, } \hat{\mu})}$$

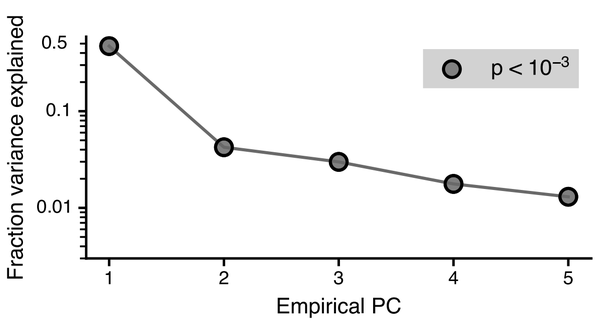
Individual-subject modeling of functional connectivity

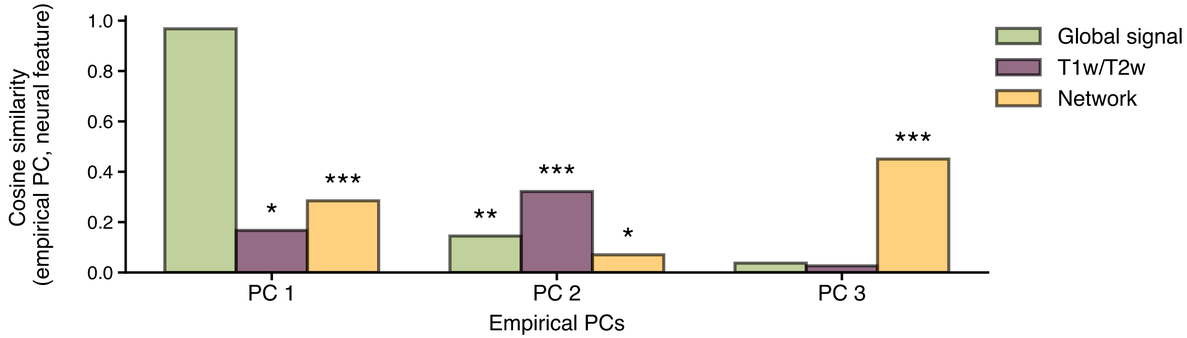


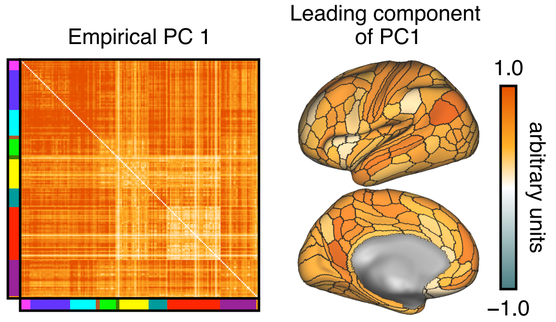


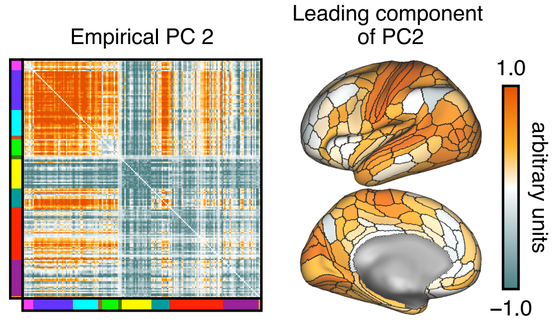
Modes of population variation

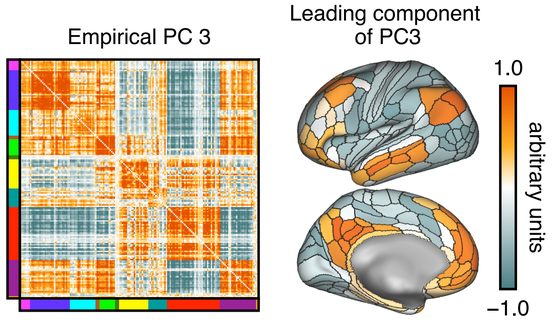


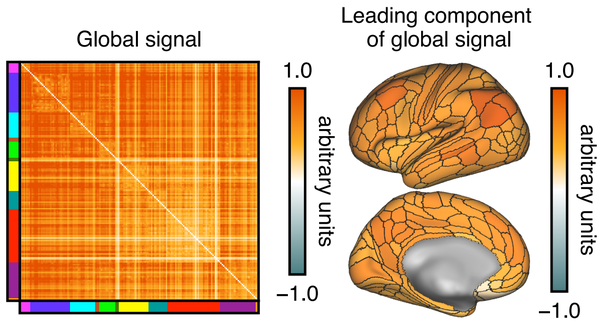


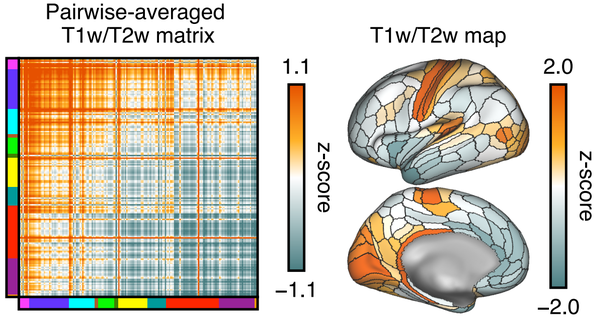


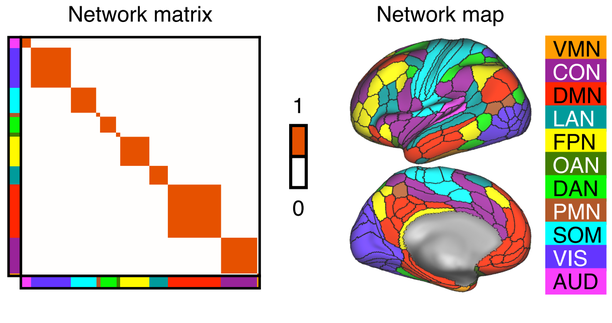




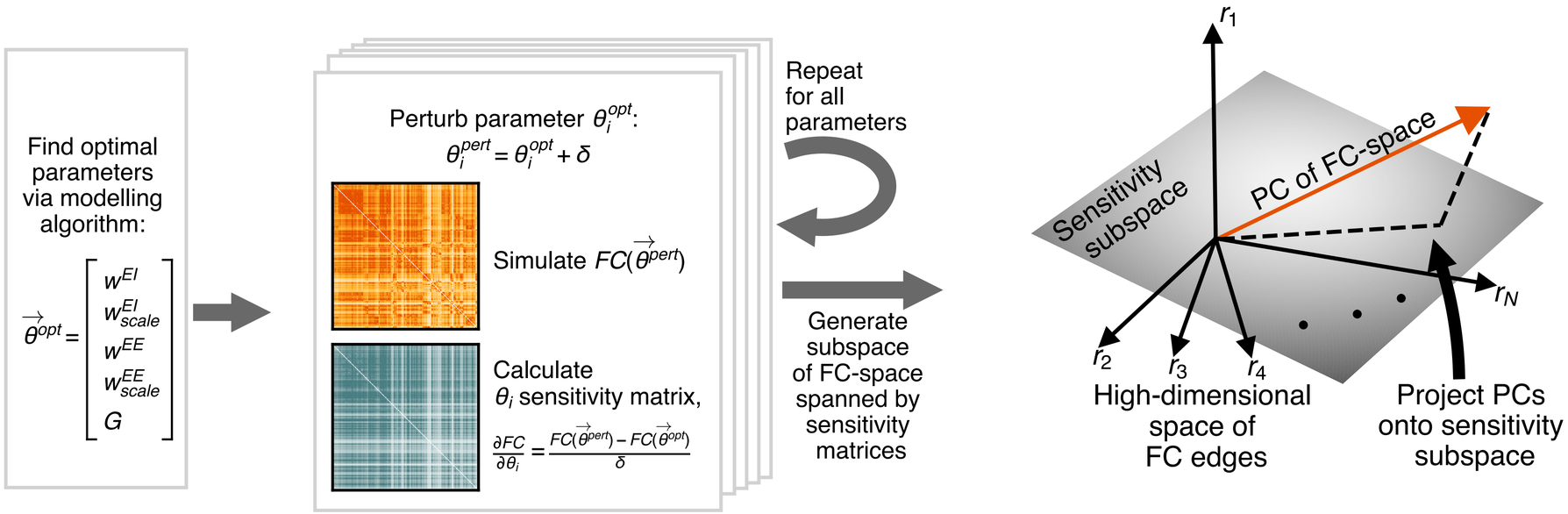


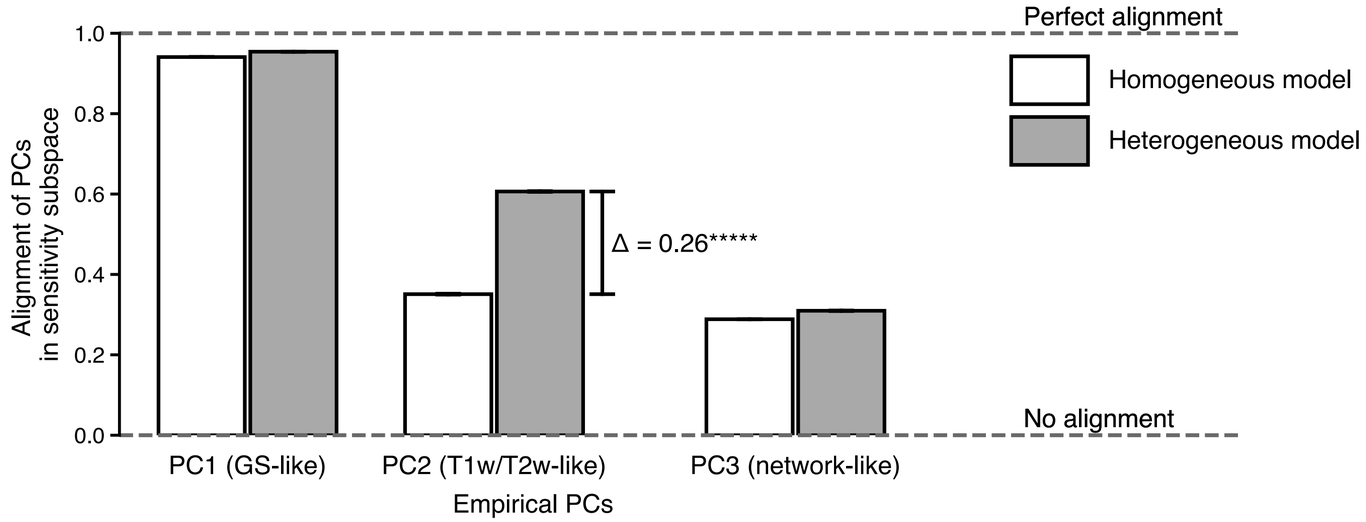






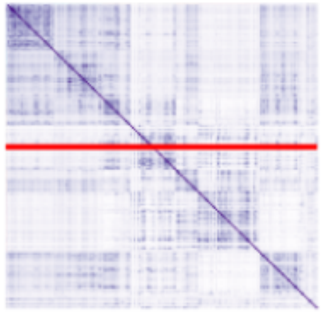
Model expressivity to capture modes of population variation



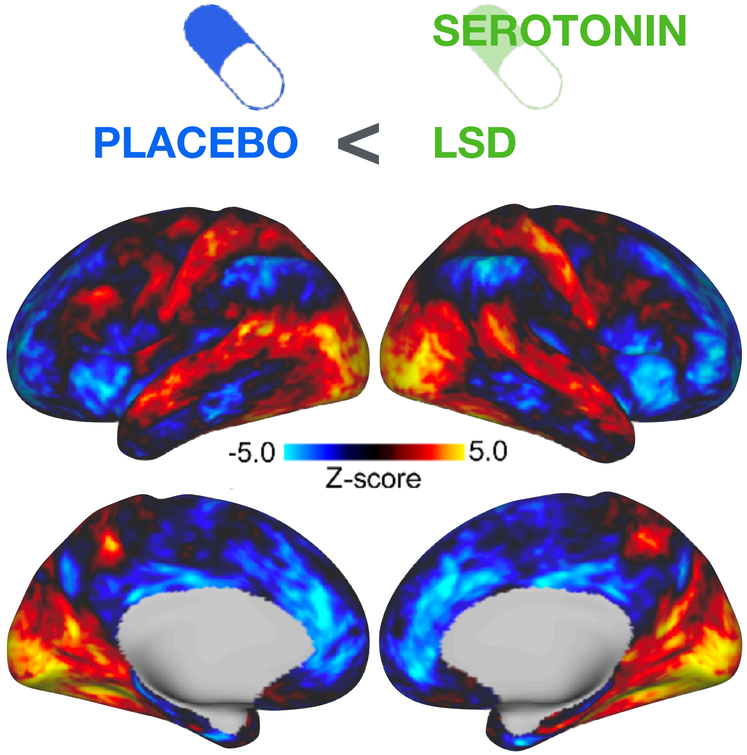


LSD effects on resting-state functional connectivity

Global Brain Connectivity (GBC)



$$GBC_i = \frac{1}{N}\sum_{j=1}^{N} FC_{ij}$$



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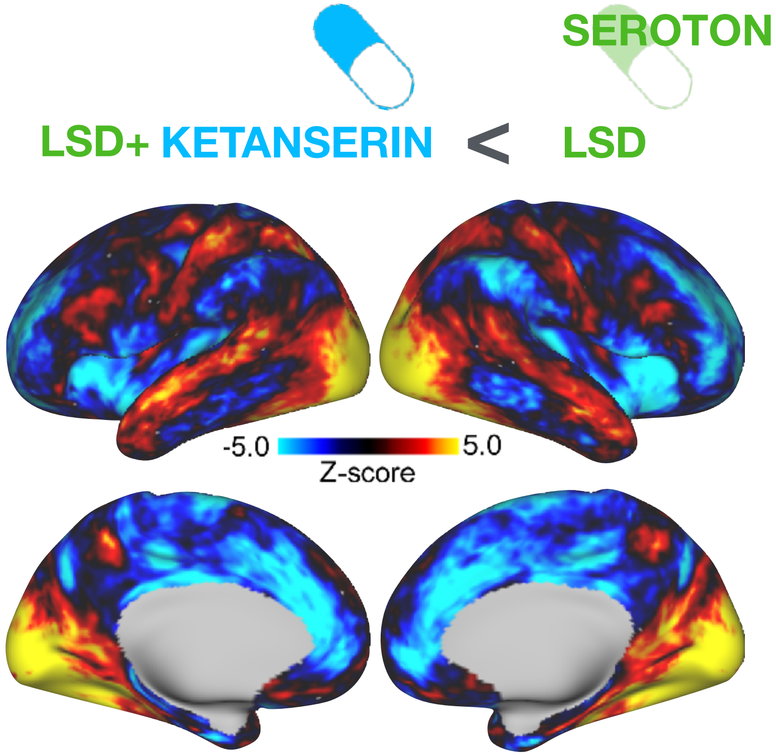


Katrin Preller
Univ. of Zurich

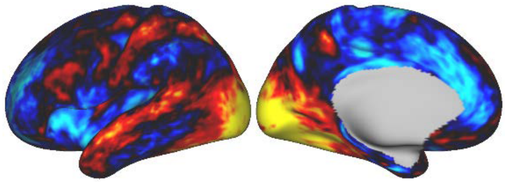
- Neural and behavioral effects of LSD blocked by ketanserin, a selective antagonist of the serotonergic **5-HT2A** receptor
- Hypothesis: map aligns with expression of gene **HTR2A**

Preller K, et al. (2018) *eLife*

Identifying molecular candidates of neuroimaging effects

Josh Burt

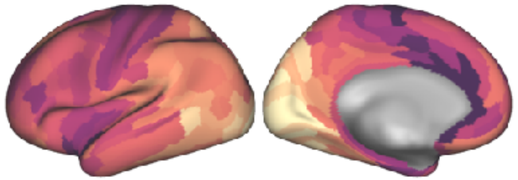
LSD ΔGBC map



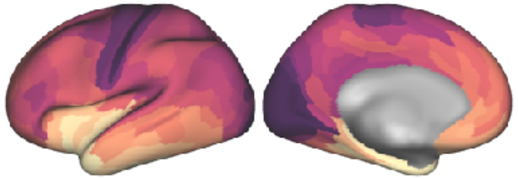
Correlation

Gene expression maps

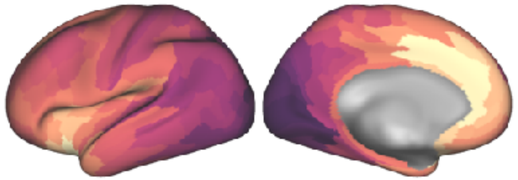
HTR2A

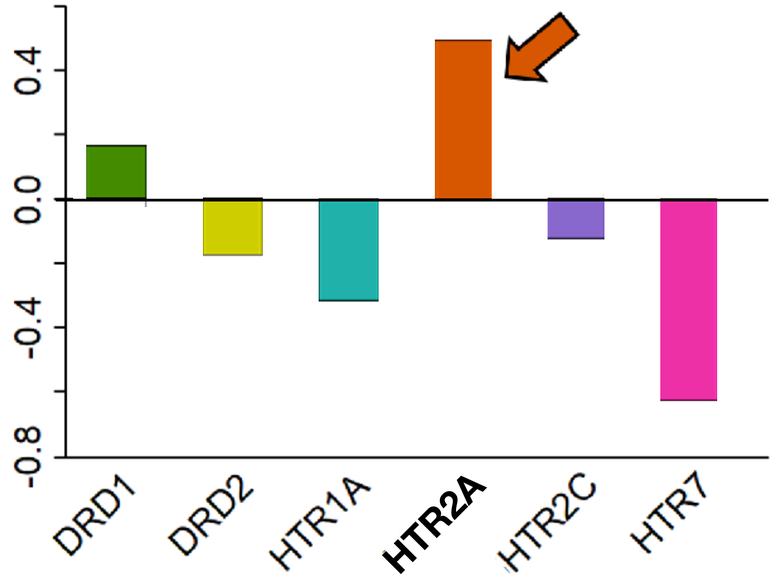


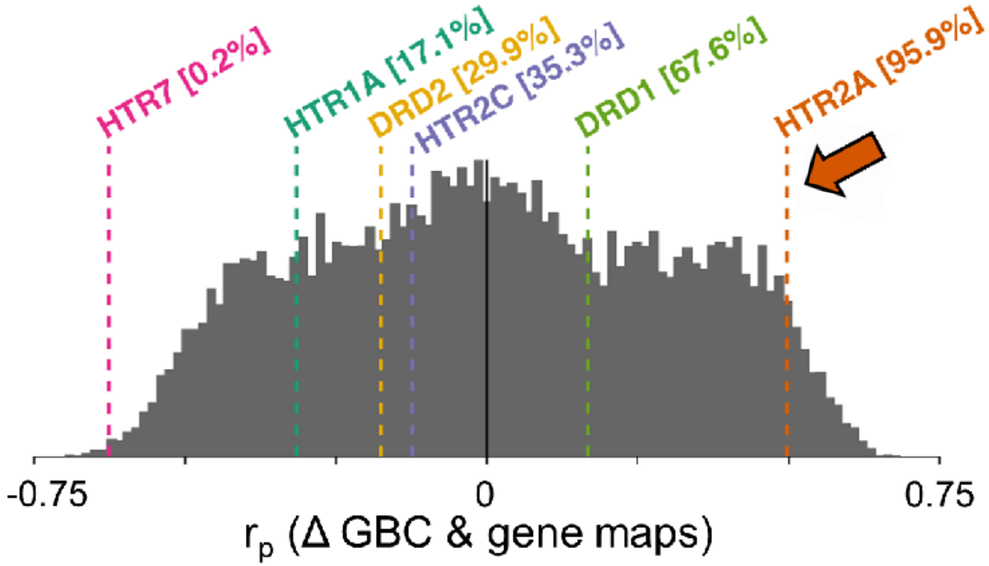
HTR1A



HTR7

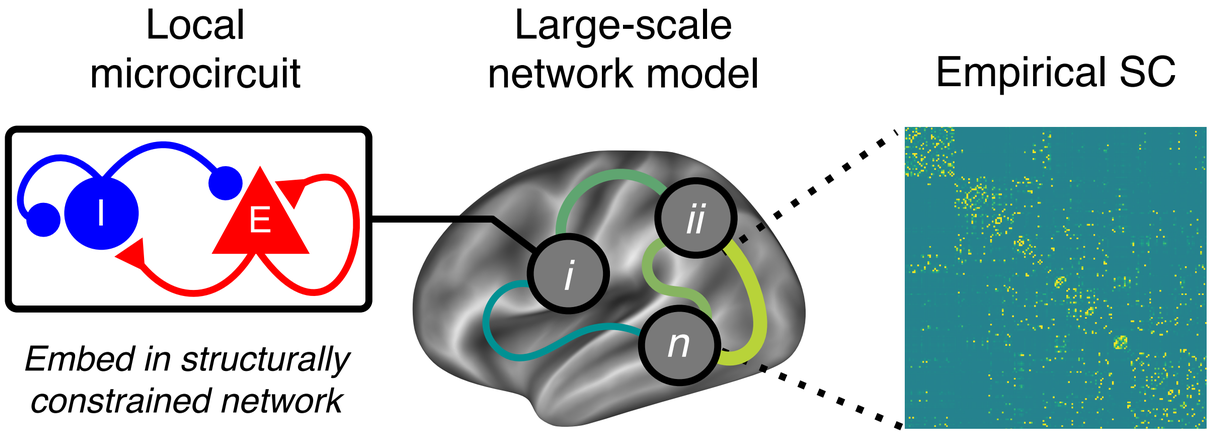


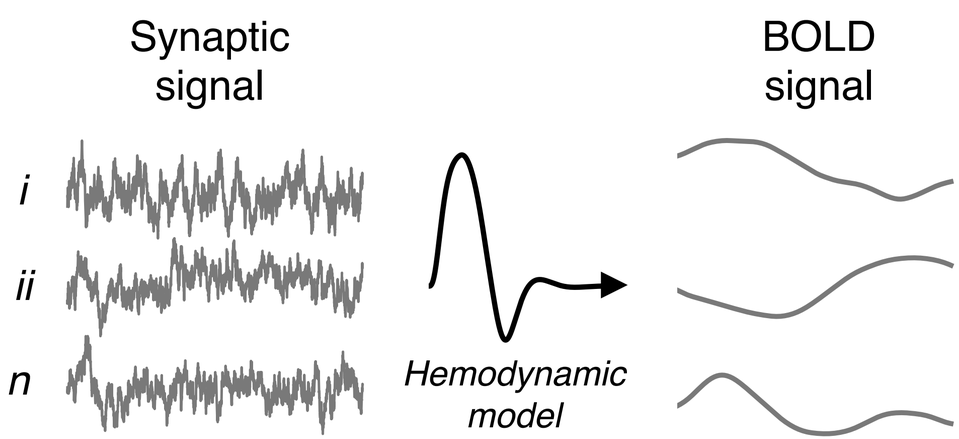


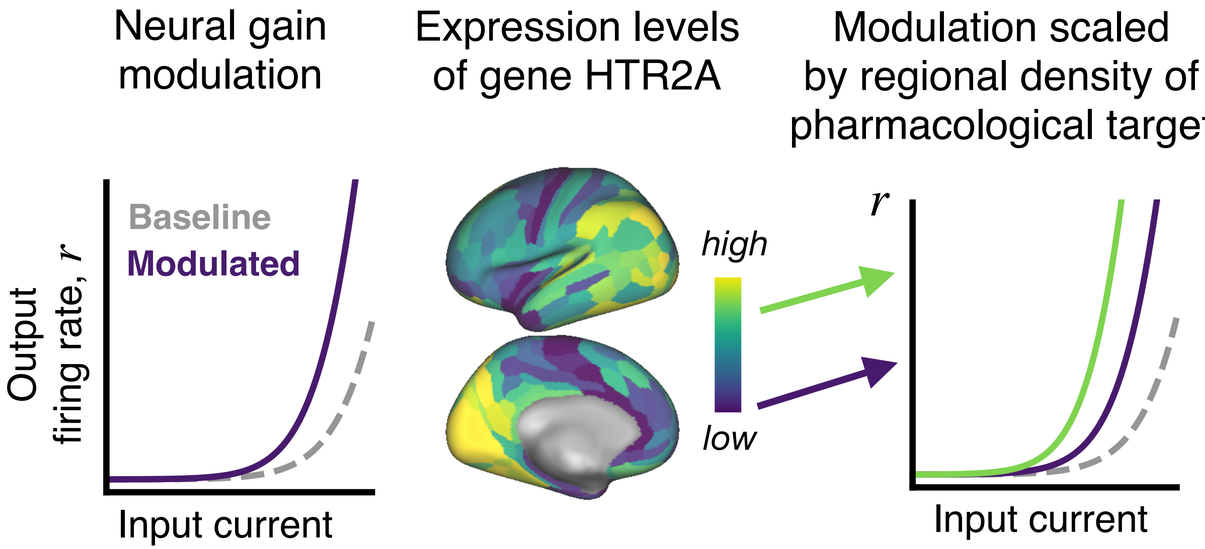


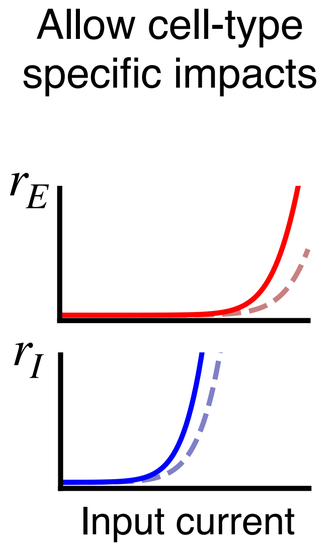
Preller K, et al. (2018) *eLife*

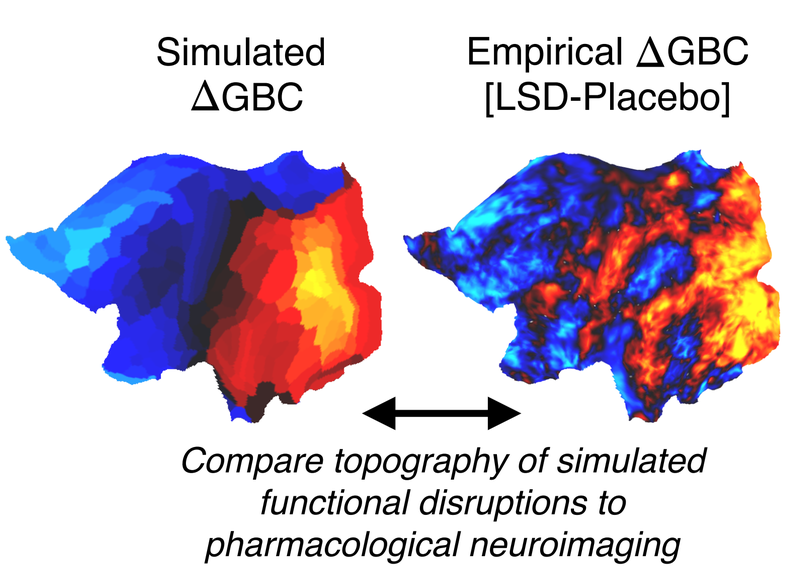
Modeling pharmacological neuroimaging



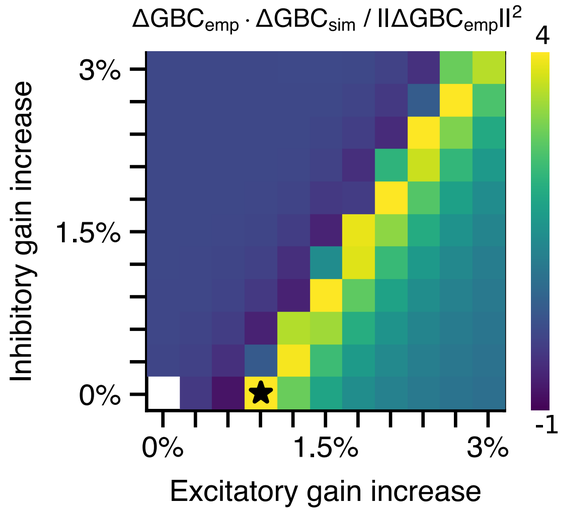


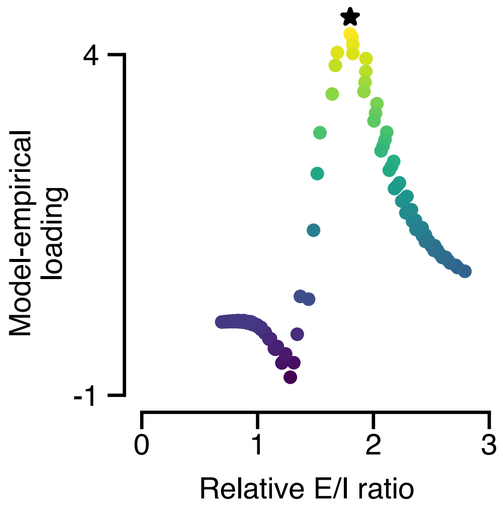


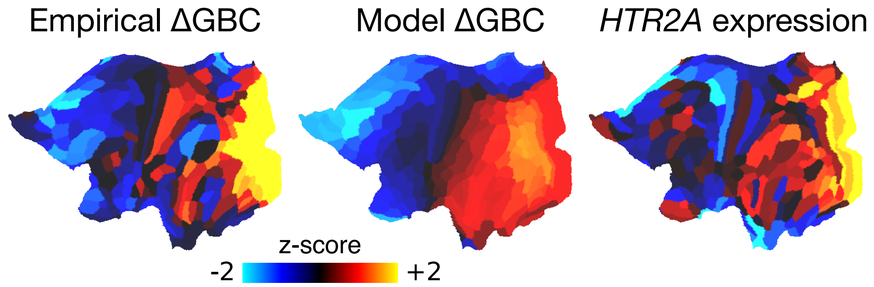


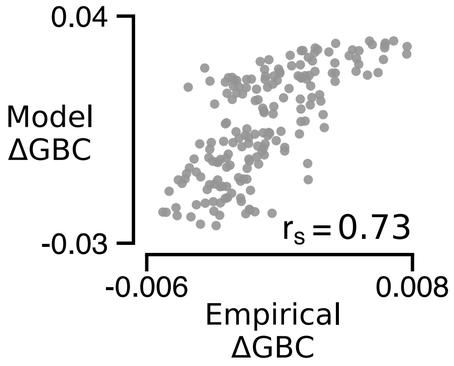


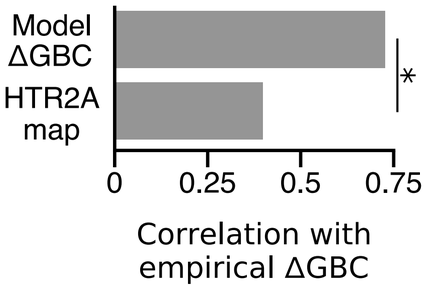
Model captures topography of LSD-induced connectivity changes via HTR2A-mediated gain modulation

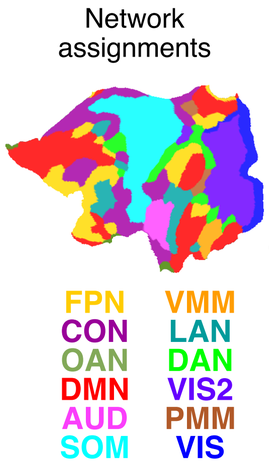


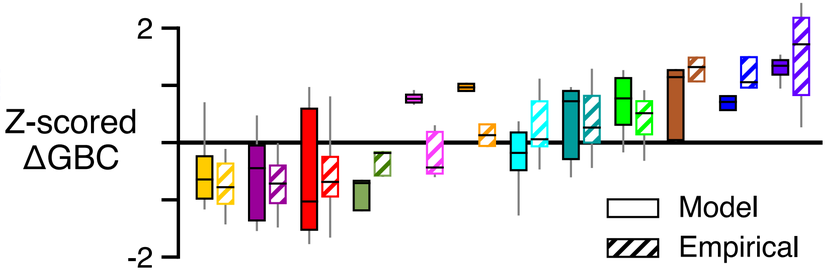


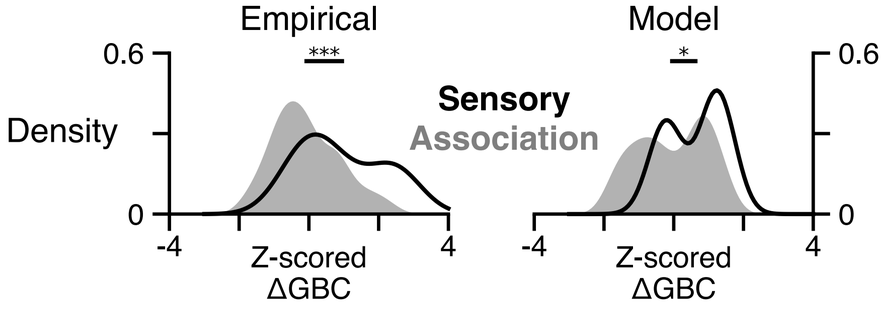












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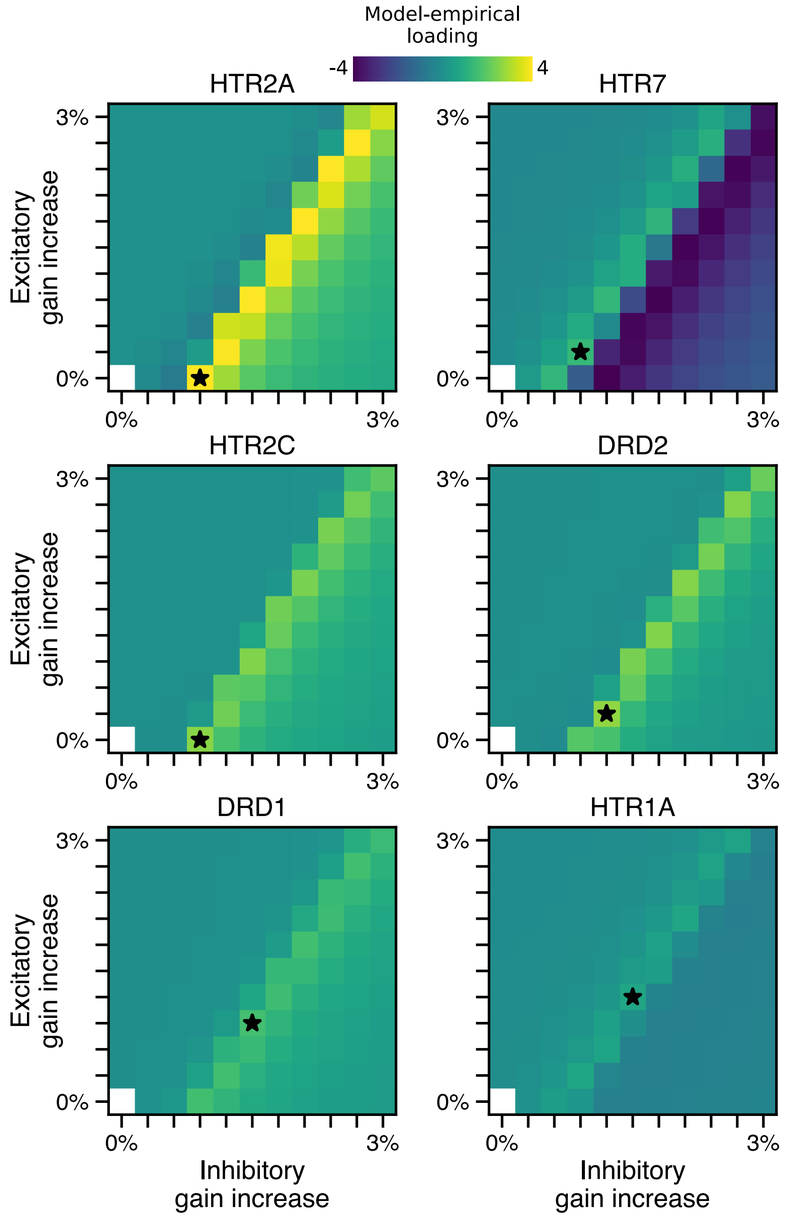
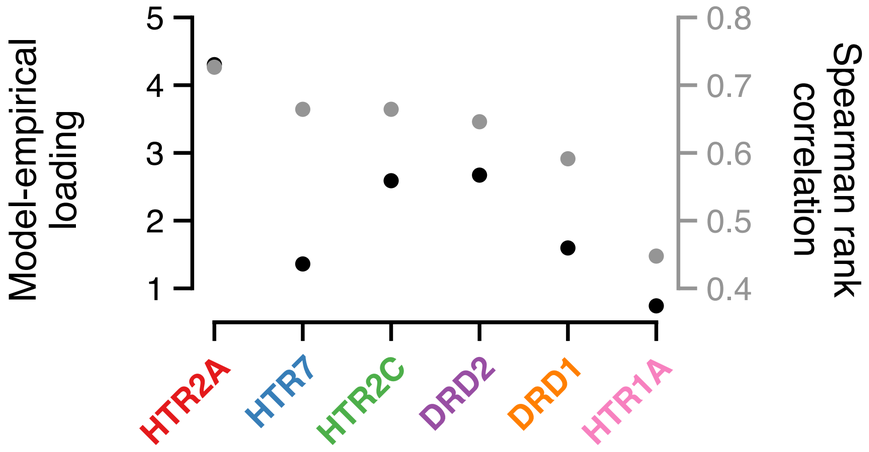
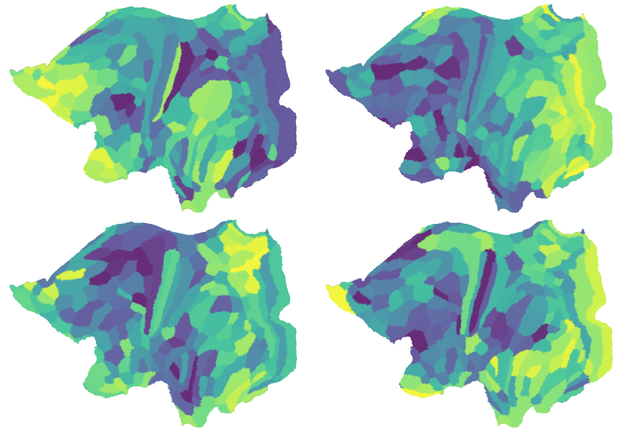
Comparison of HTR2A to alternative gain modulation maps

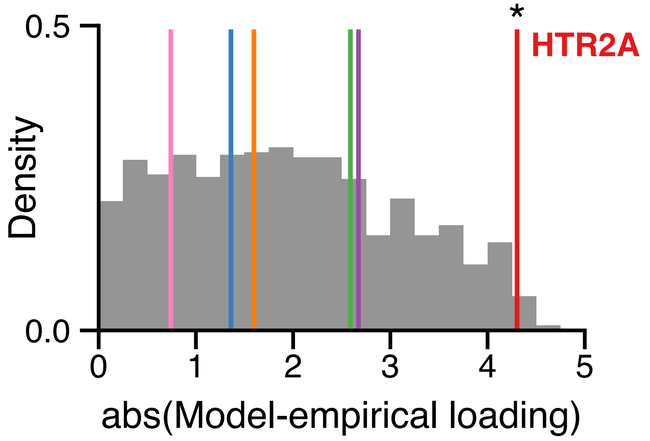




Spatial autocorrelation-preserving surrogate maps



Spatial autocorrelation-preserving surrogate map-derived null distribution



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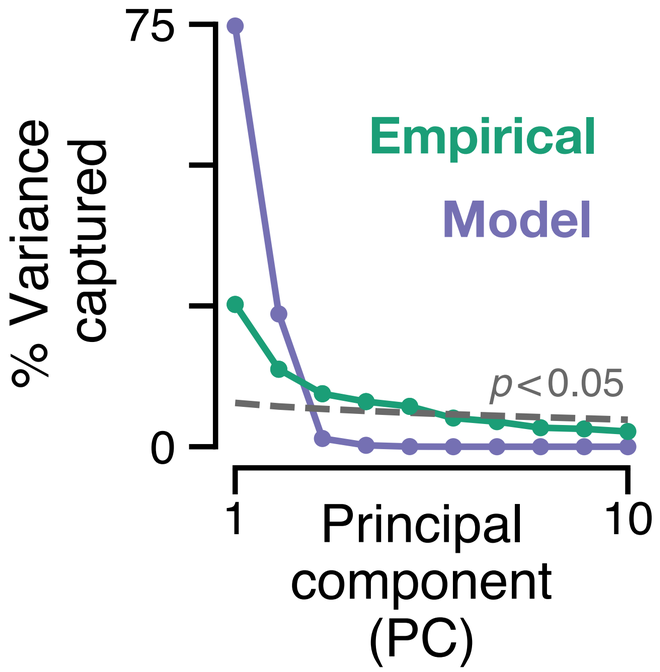
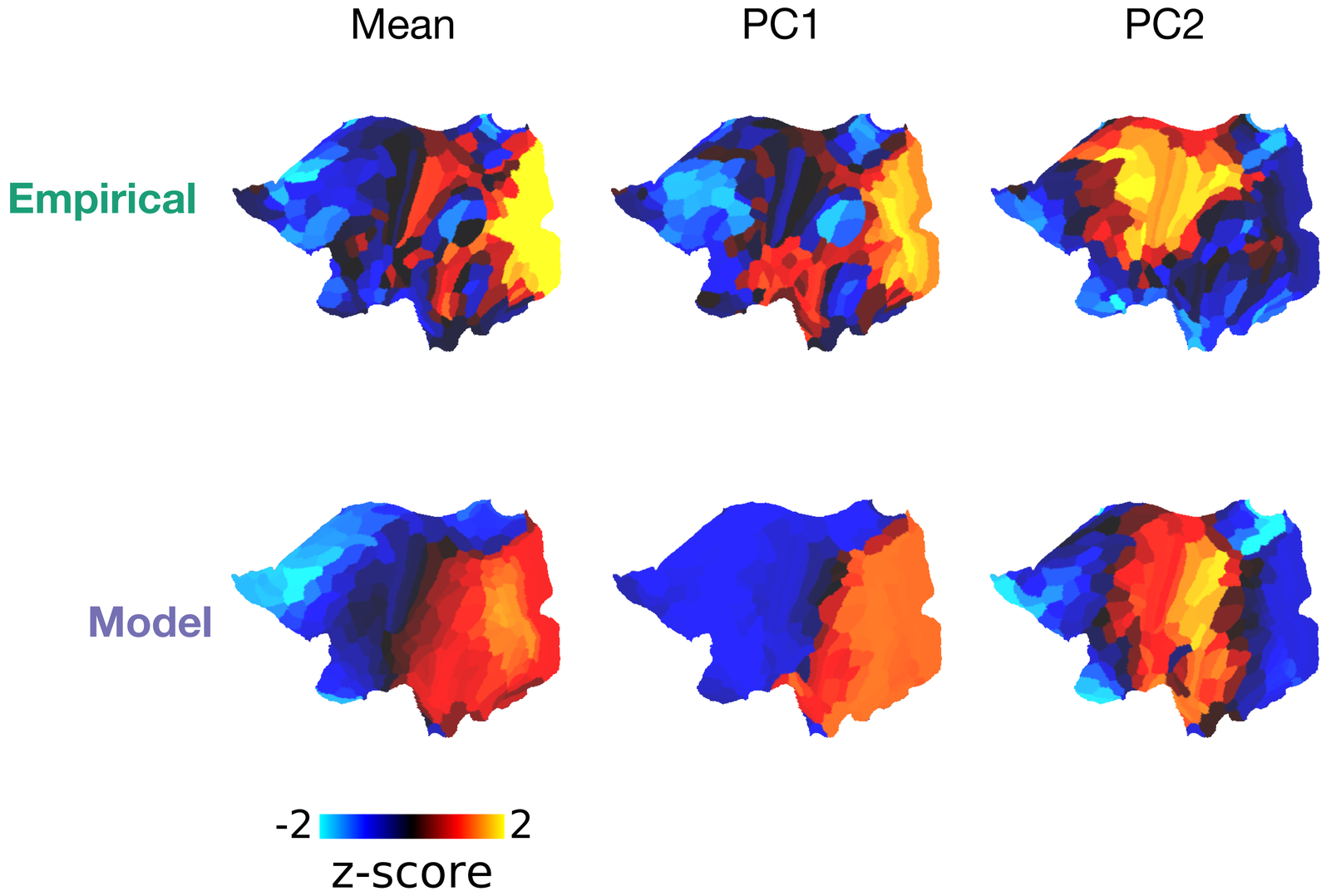
Individual variation in pharmacological fMRI response





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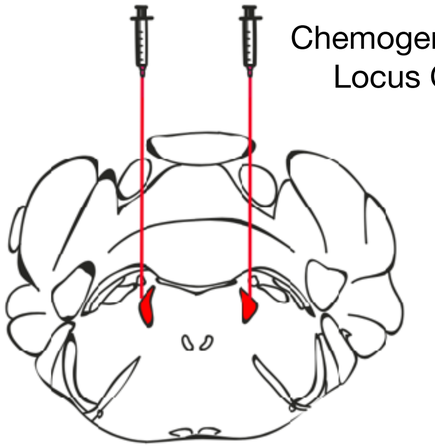
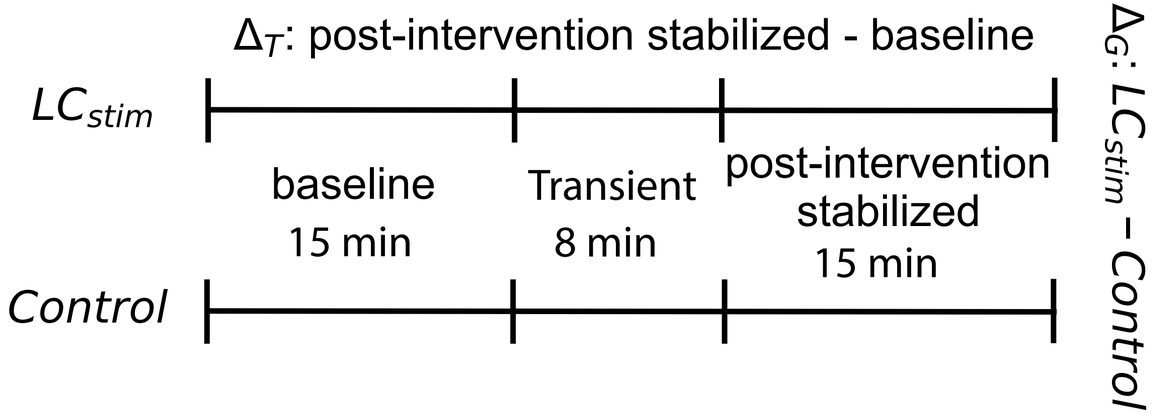
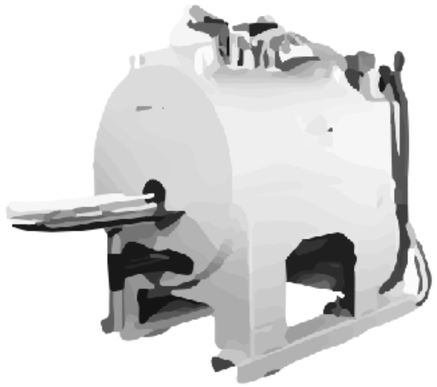
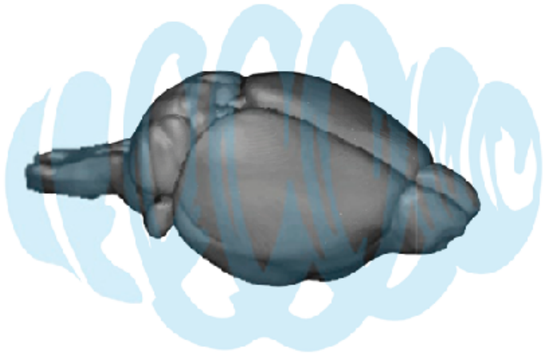
Chemogenetic activation of locus coerulus (LC) in mouse to study brainwide neuromodulation by norepinephrine



Chemogenetic activation of Locus Coeruleus (LC)



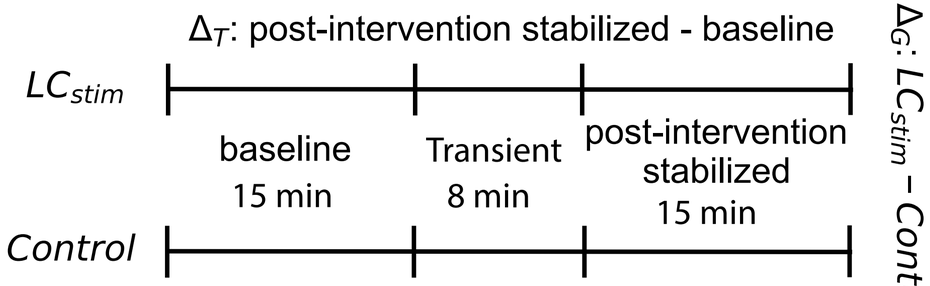


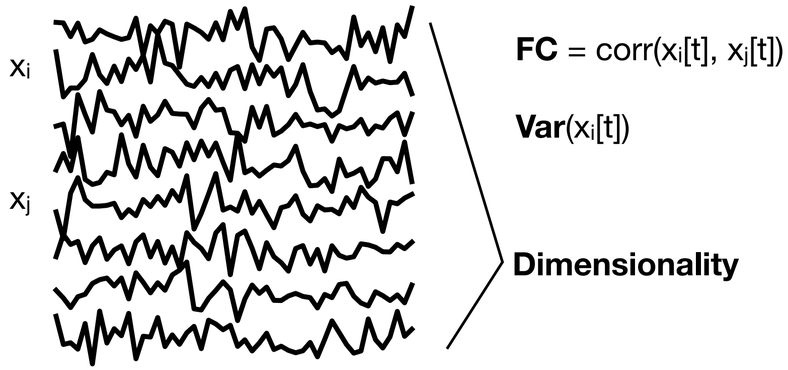


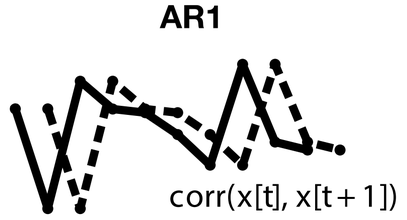
Collaboration with Valerio Zerbi (ETH)

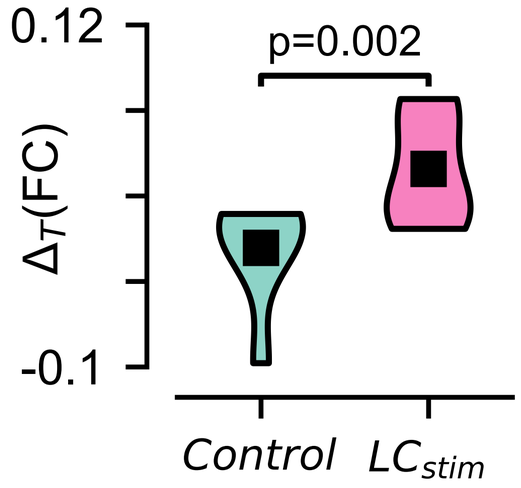
Zerbi et al. (2019) *Neuron*

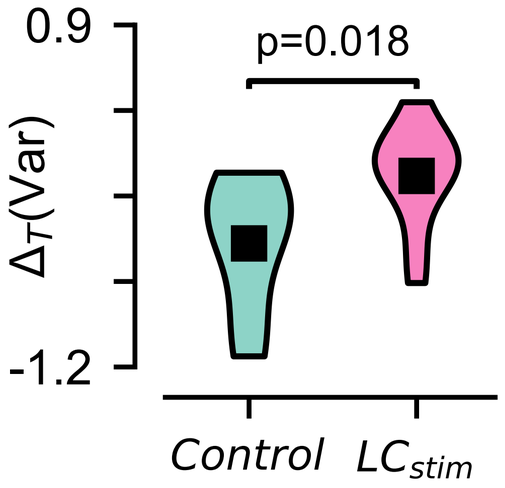
LC stimulation effects on BOLD dynamics

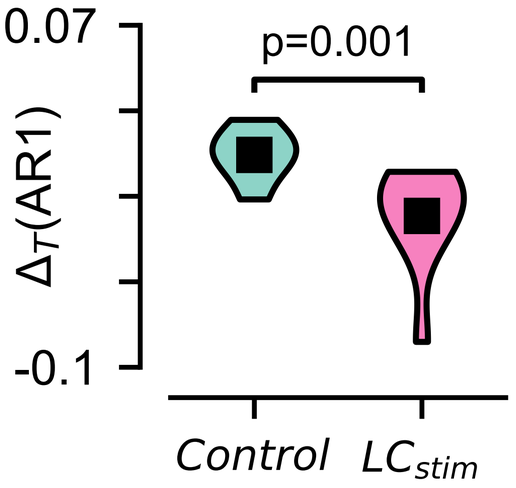


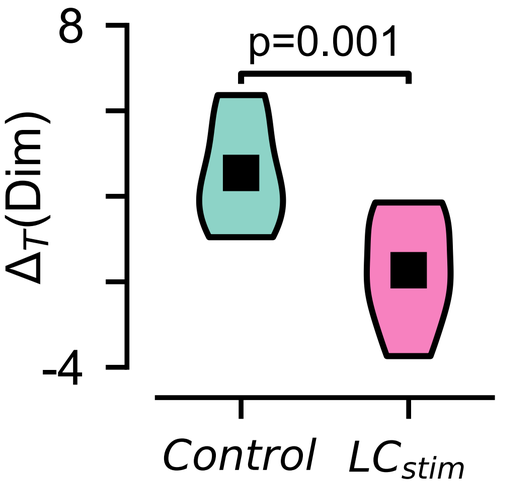




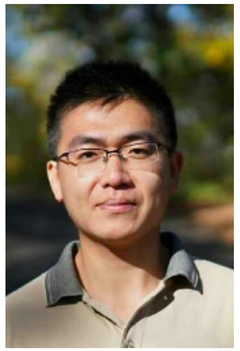






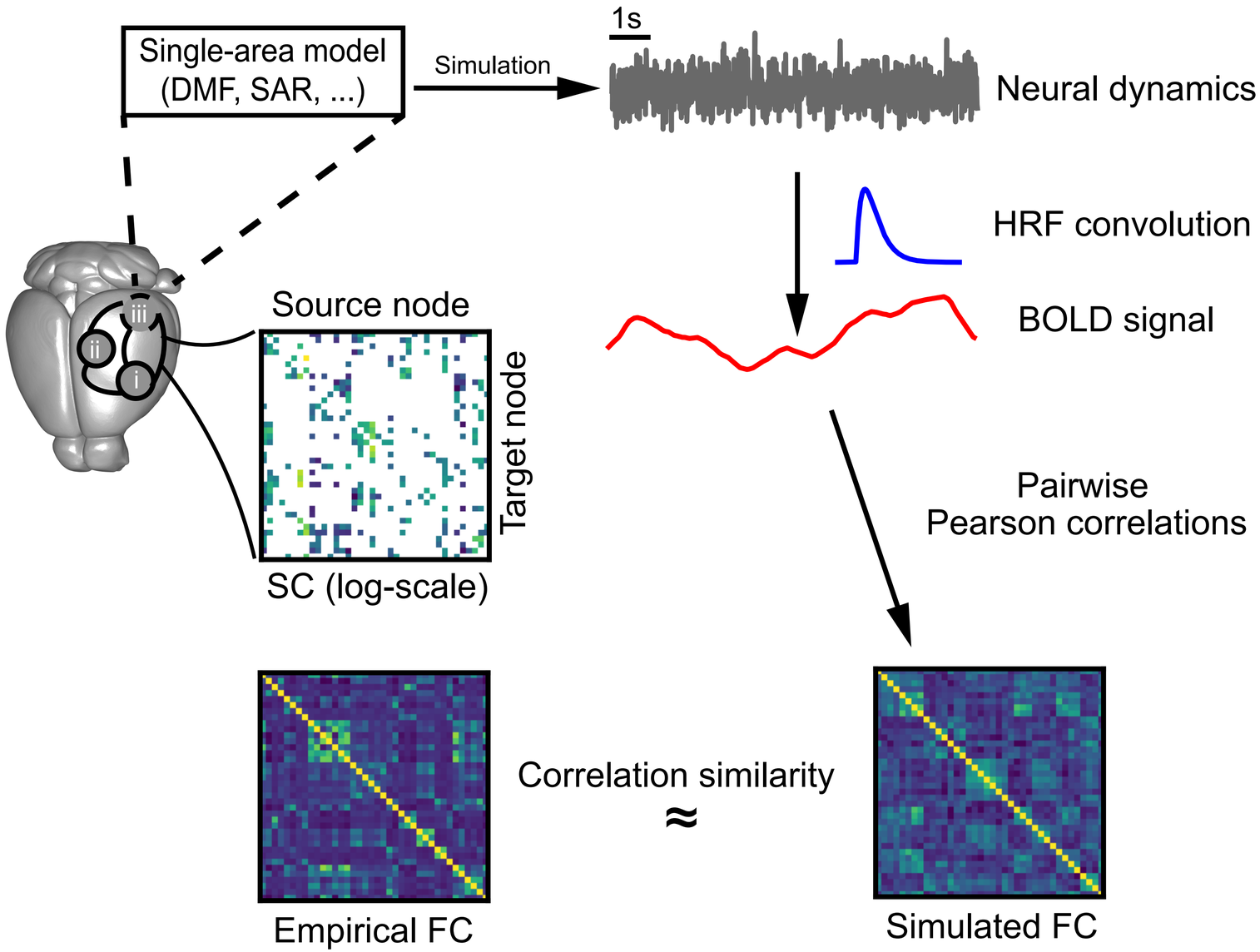


Large-scale model of mouse cortical BOLD dynamics

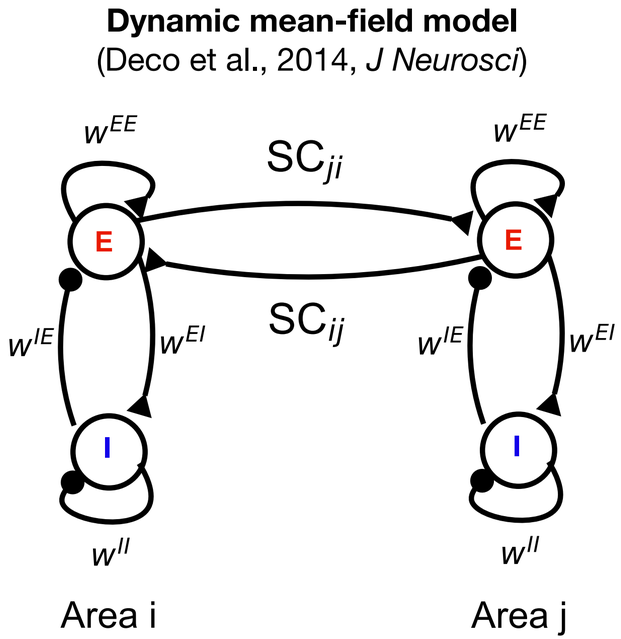


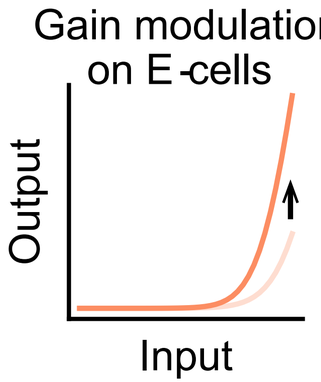
Daming Li

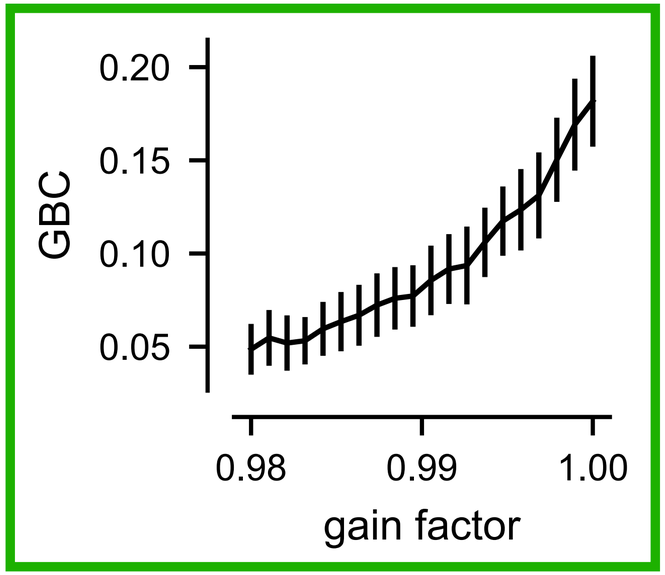
Qinglong Gu

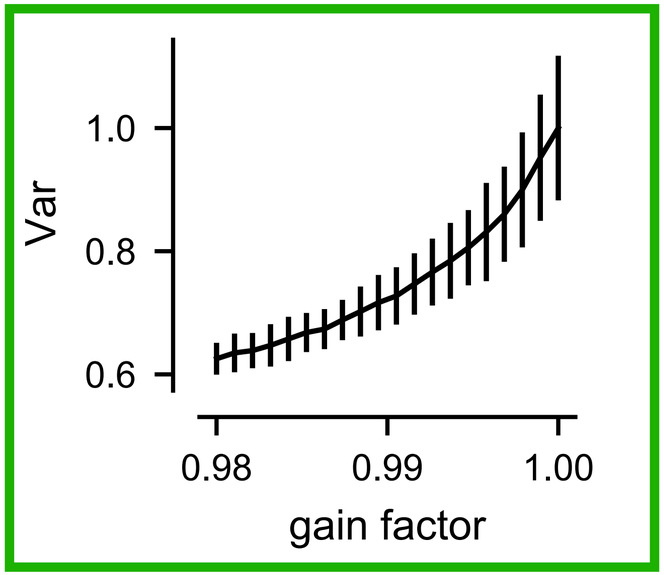


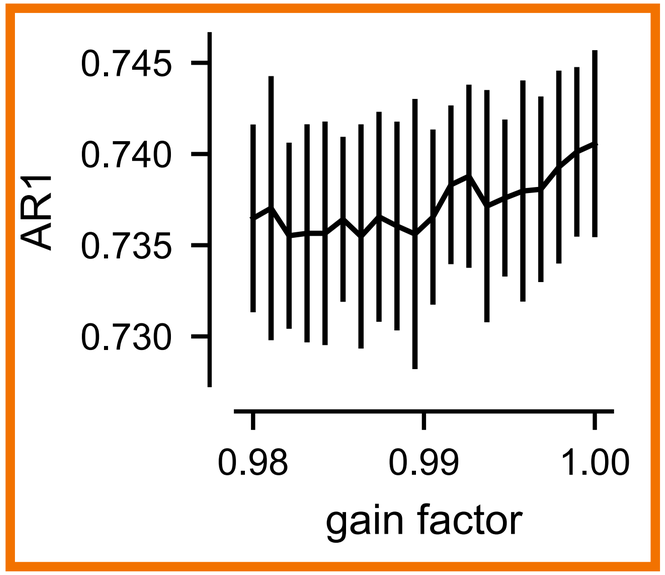
Dynamic mean-field model of mouse cortex with gain modulation

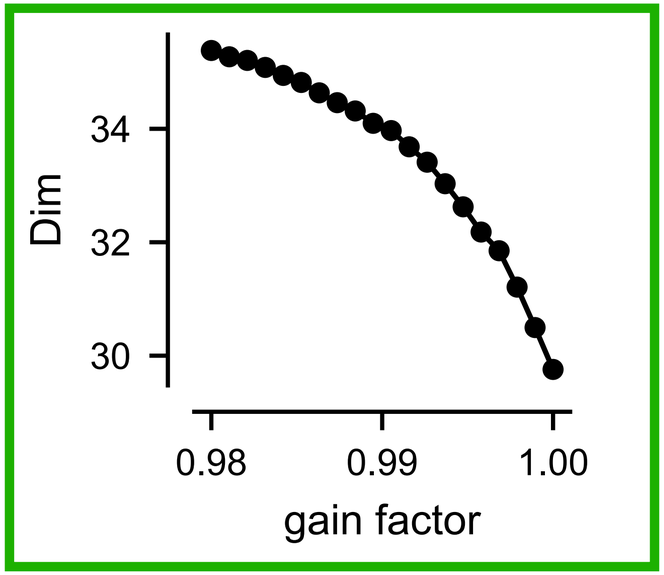




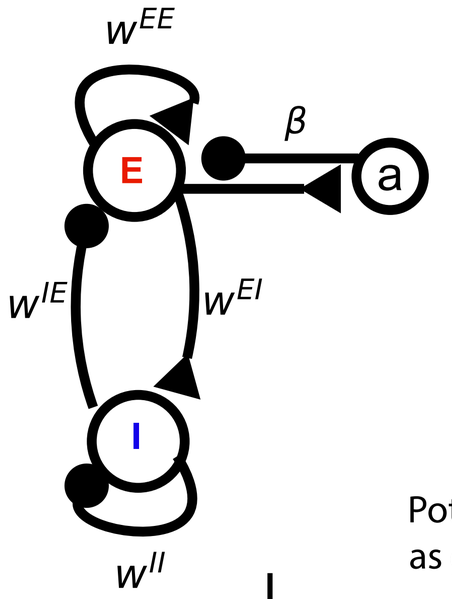


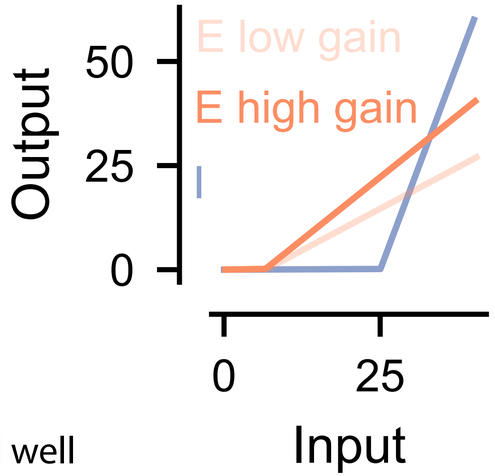


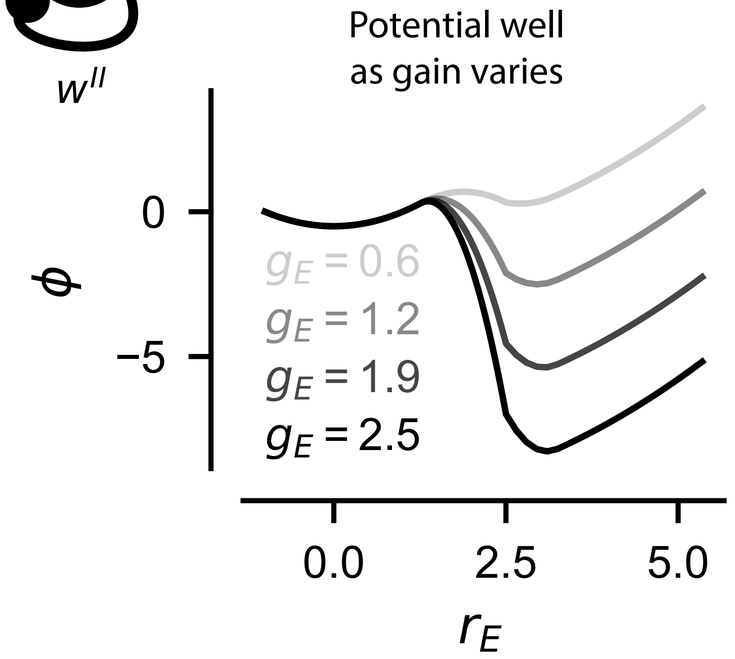


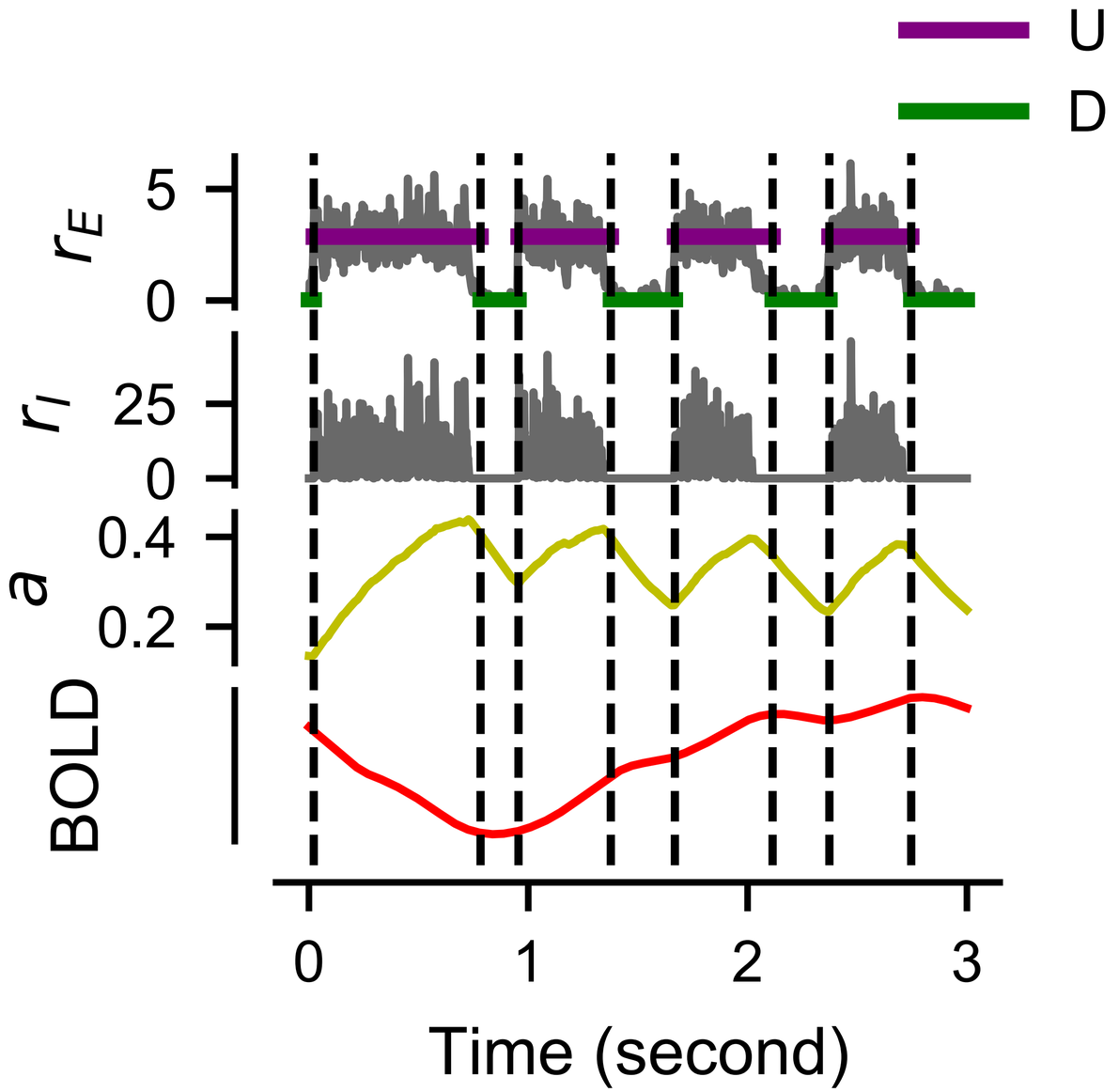


Local E-I circuit with adaptation with bistable dynamics

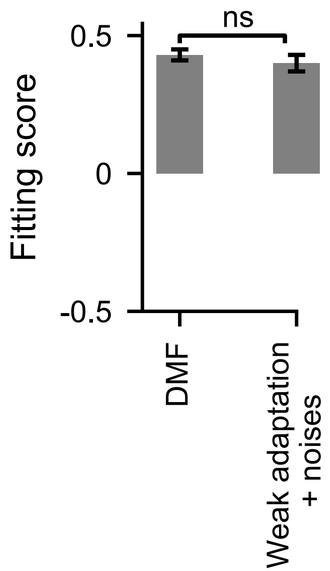


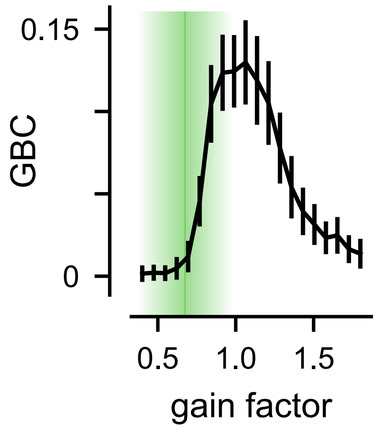


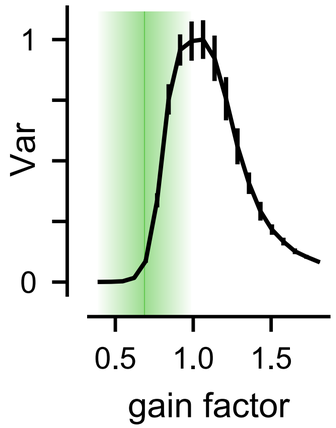


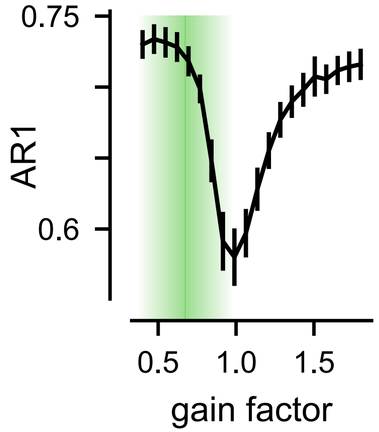


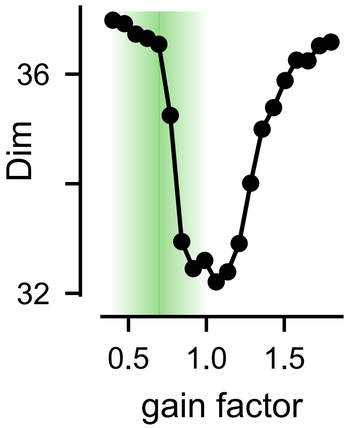
Gain modulation in bistable model captures LC stimulation effects

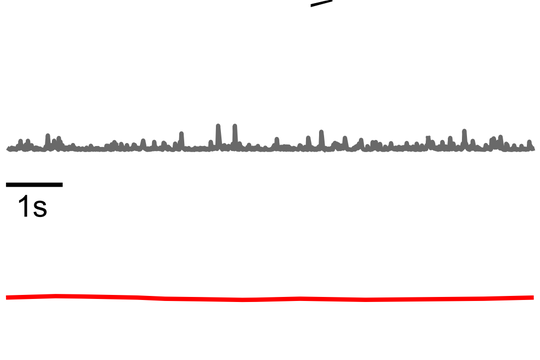






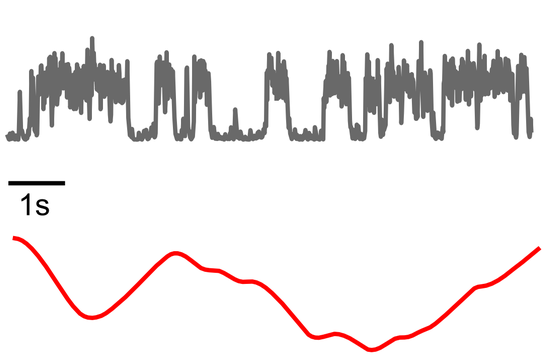






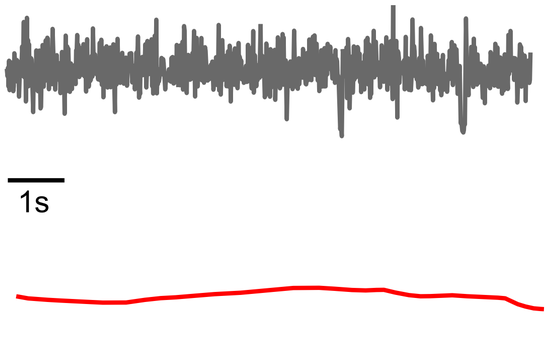
Low gain

Local noise dominate
High AR1, low variance



Medium gain

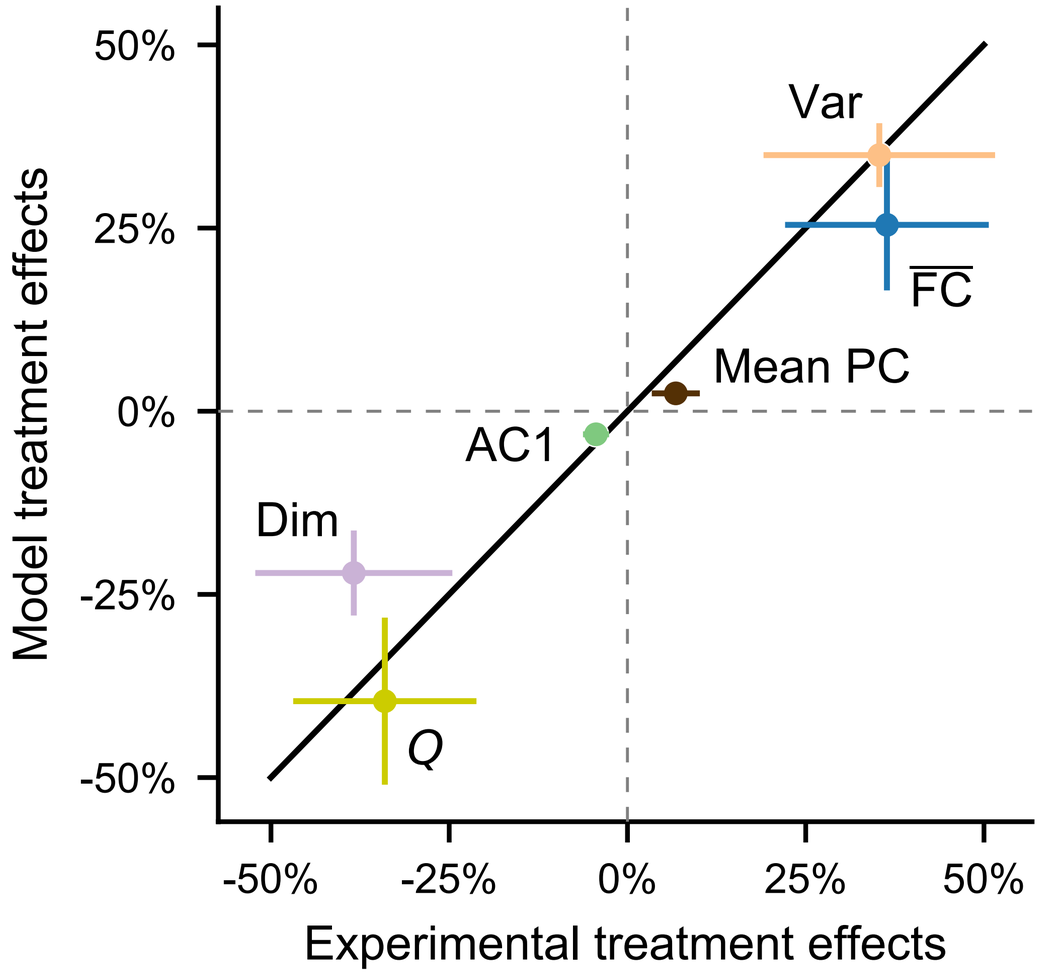
Macroscopic transitions dominate
Low AR1, high variance



High gain

Local noise dominate
High AR1, low variance

Gain modulation in bistable model captures LC stimulation effects

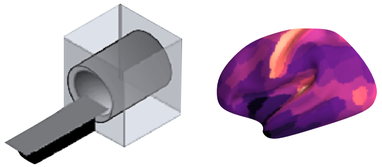


- When the local node is in a suitable regime of stochastic bistable dynamics, then multiple neural features of LC stimulation are produced under gain modulation of excitatory neurons

Conclusions

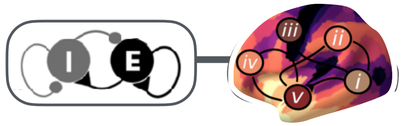
PERSONALIZED BEHAVIORAL PROFILES

NEURAL BIOMARKERS

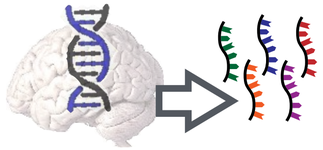


PHARMACOLOGICAL NEUROIMAGING

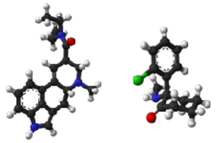
BIOPHYSICAL CIRCUIT MODELING



TRANSCRIPTOMIC MAPPING



PHARMACOLOGICAL THERAPEUTICS



- **Bridging across levels of analysis, from molecular to systems**
  - Platforms to iteratively expand and constrain computational models with biophysical detail needed for capture important empirical phenomena
  - Mapping transcriptomic expression
  - Modeling biophysical circuit dynamics at individual level
  - Modeling brainwide response to pharmacology and neuromodulation

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Qinglong Gu

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