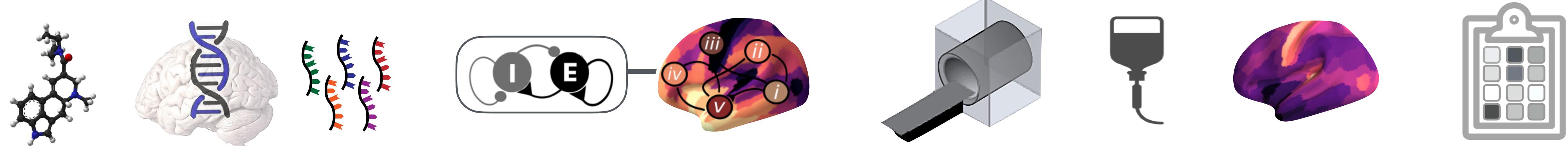


Modeling Connectivity: Biophysical Network Modeling

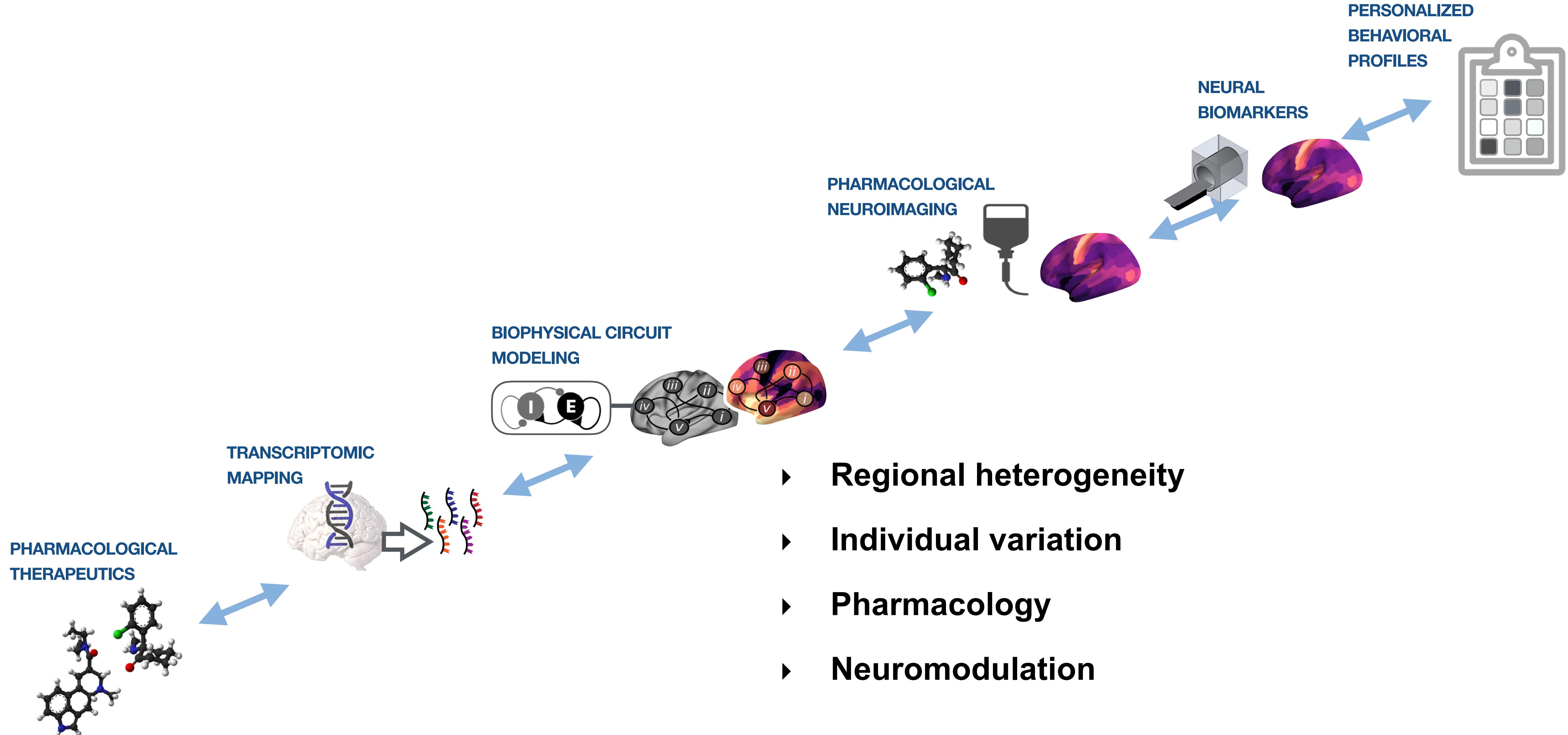


John D. Murray

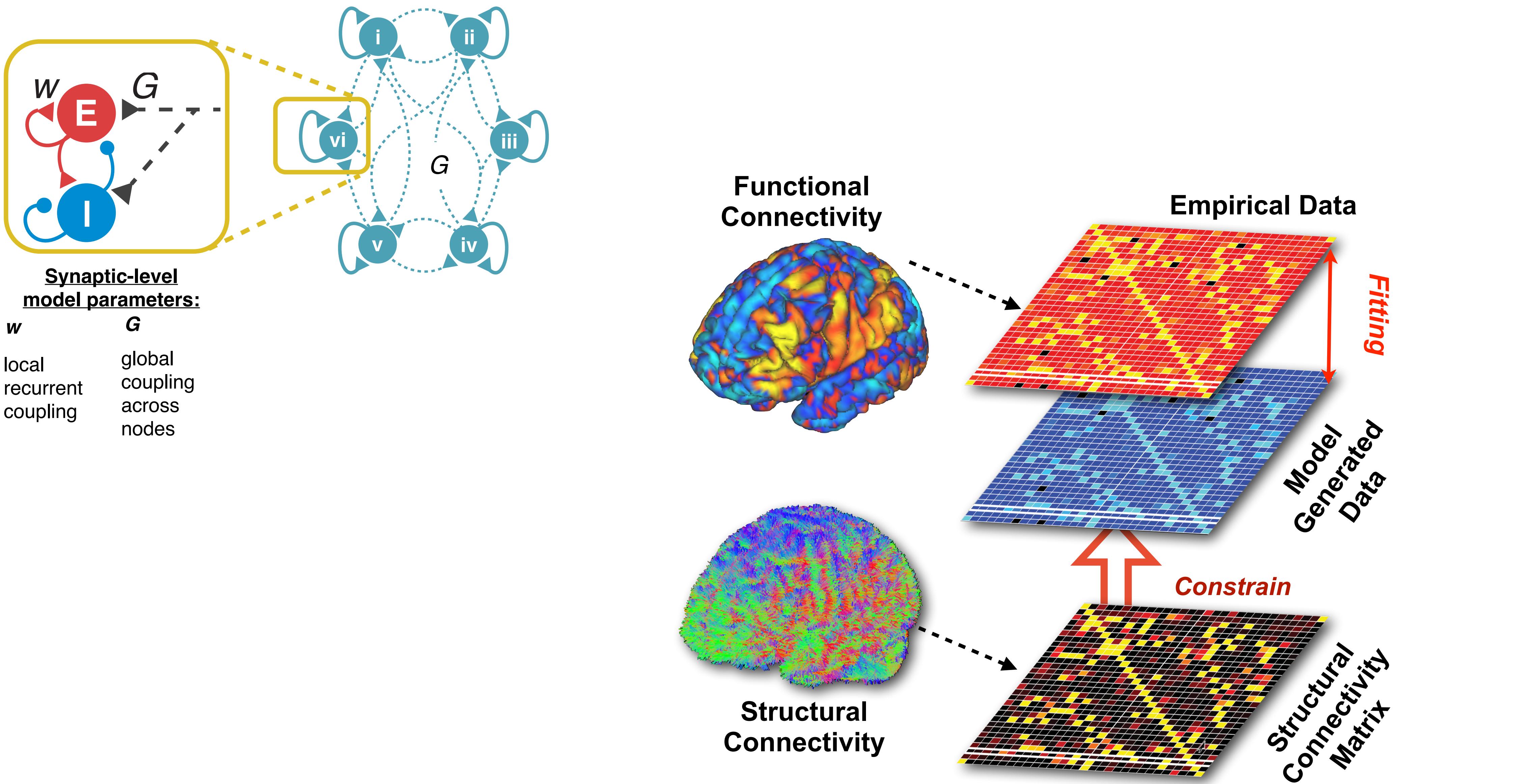


Division of Neurocognition,
Neurocomputation, and
Neurogenetics (N3)
Department of Psychiatry
Yale School of Medicine

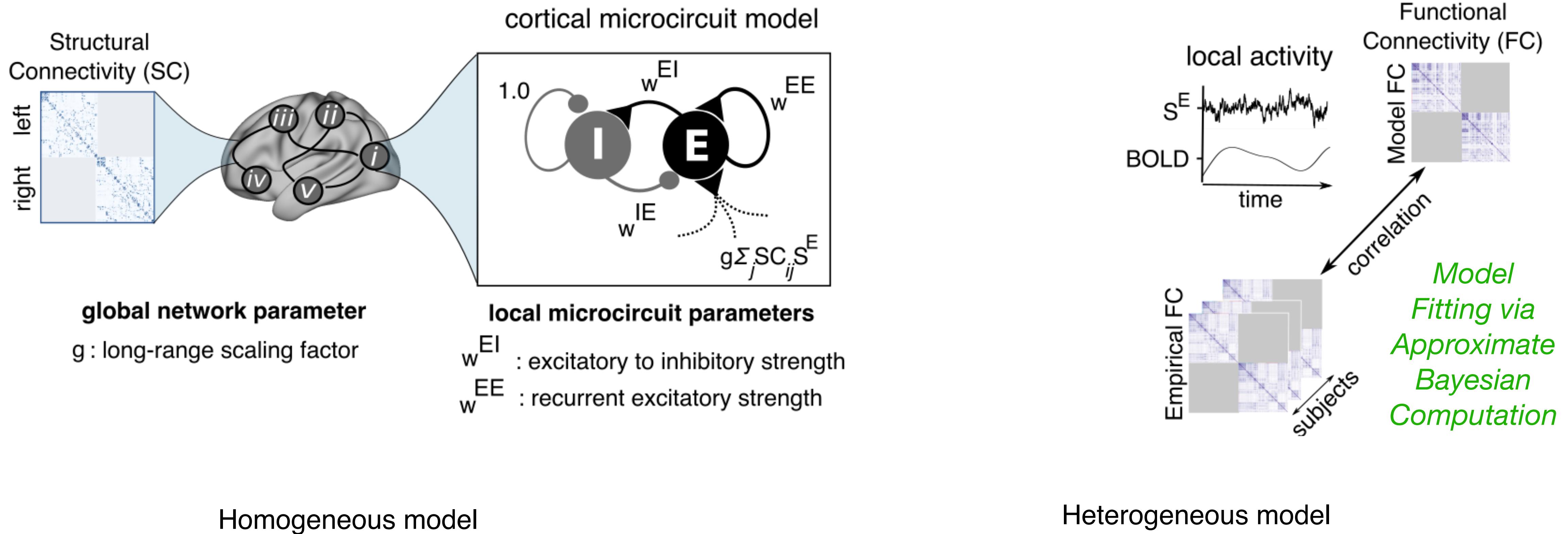
Computational Psychiatry via bridging levels of analysis with neuroimaging and neural circuit modeling



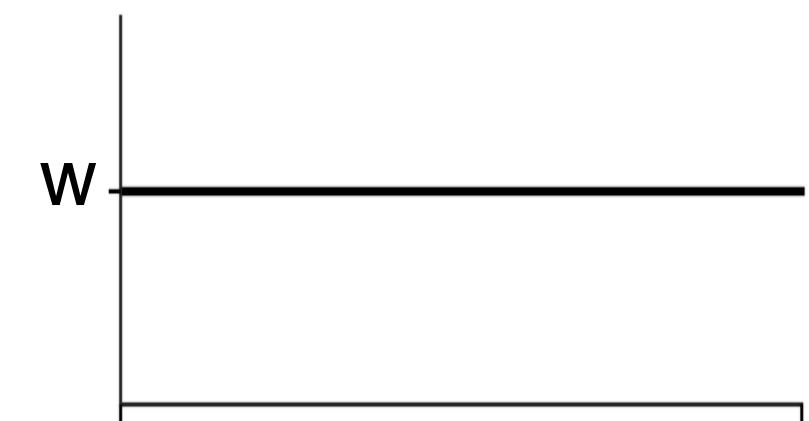
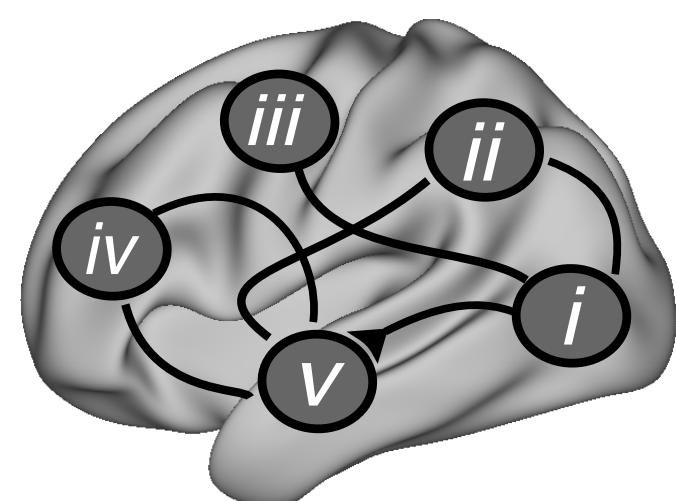
Modeling large-scale resting-state networks



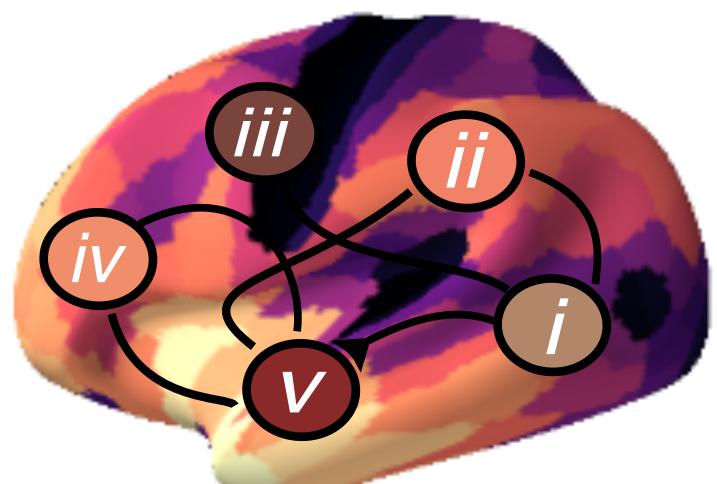
Model with heterogeneous local circuit properties



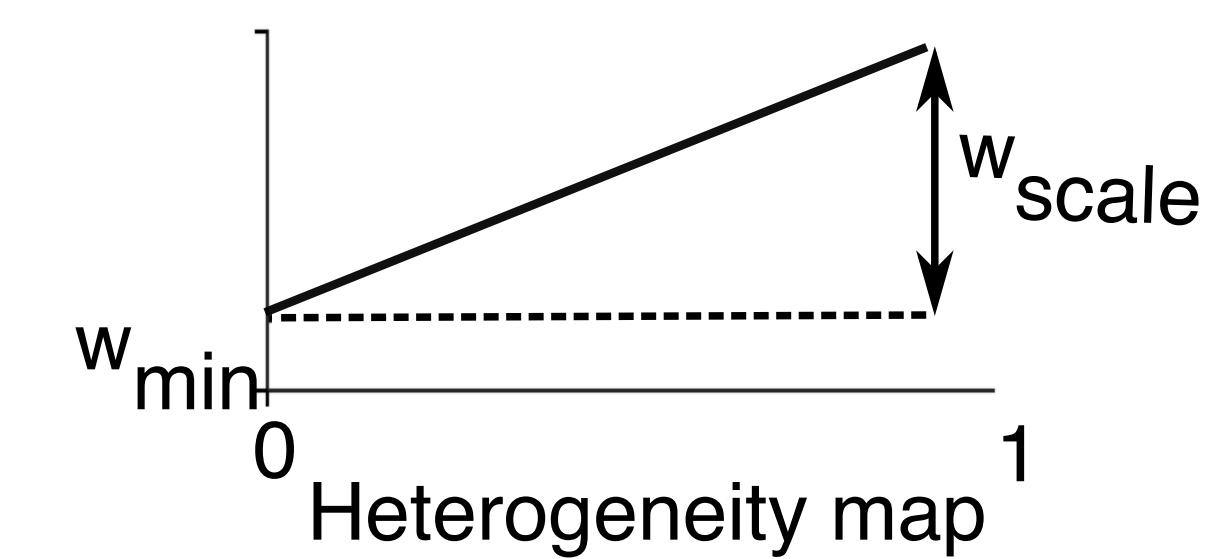
Homogeneous model



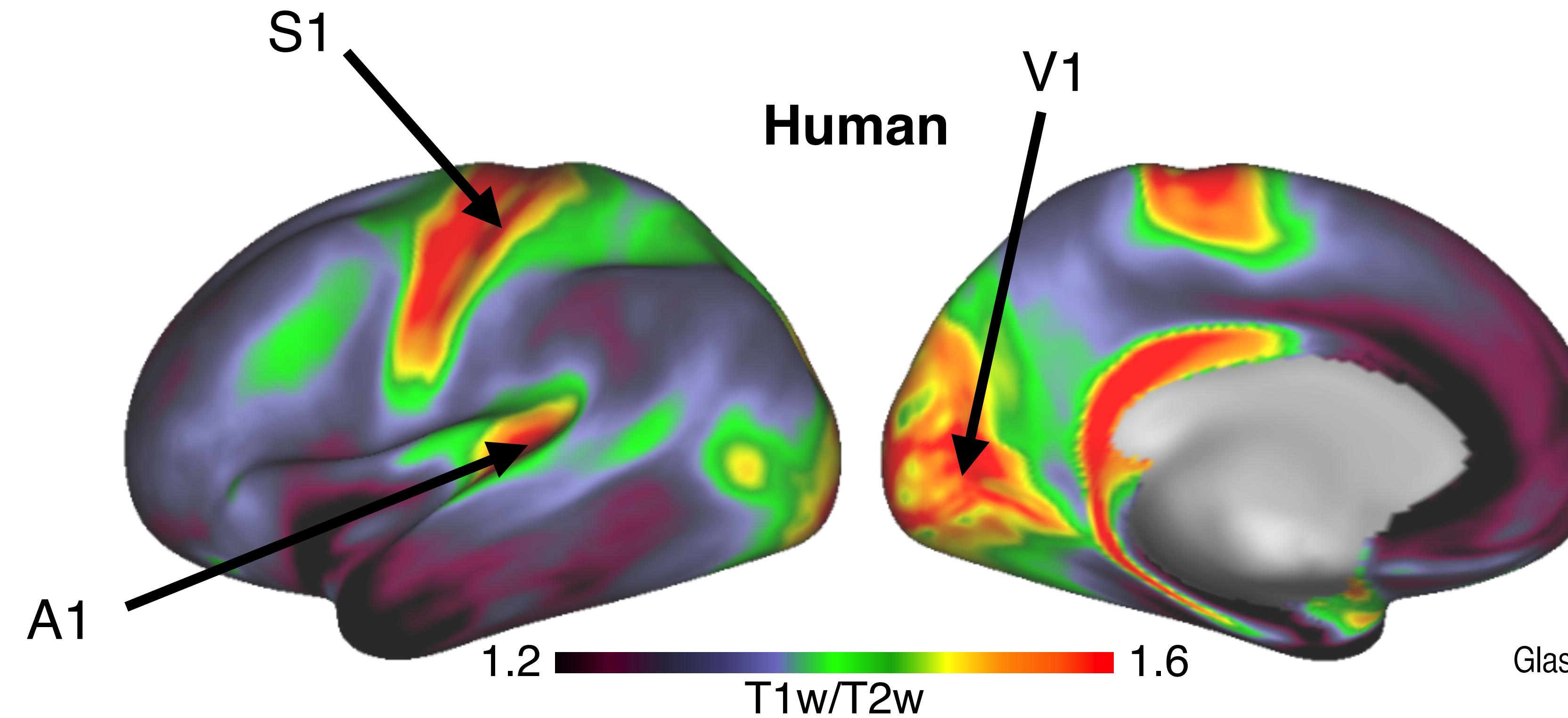
Heterogeneous model



Reverse $T1w/T2w$
myelin map



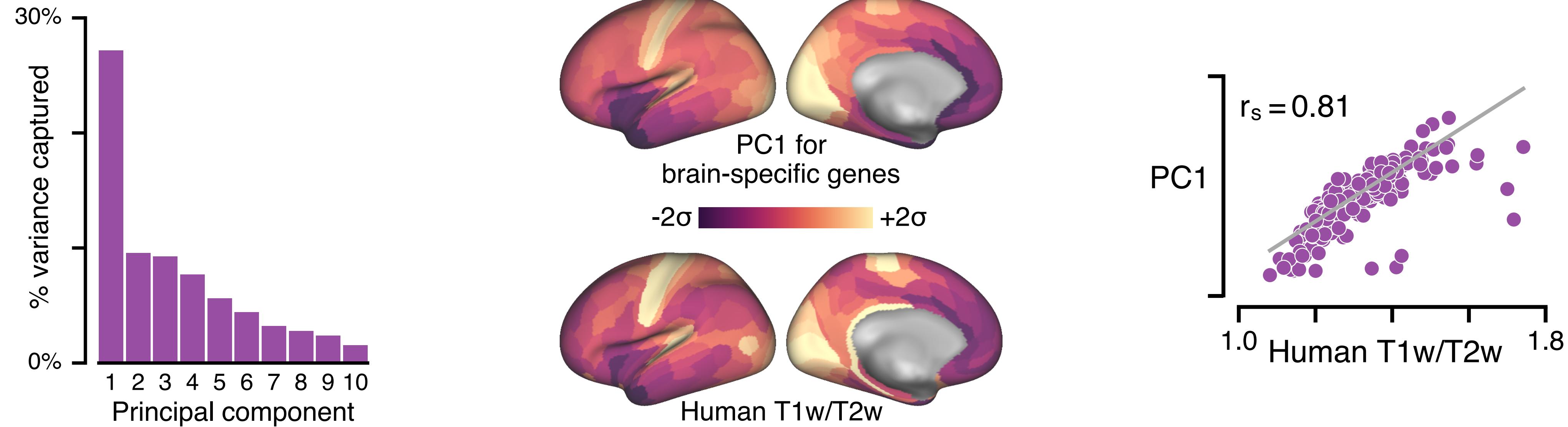
Cortical T1w/T2w map as a proxy measure for cortical hierarchy



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



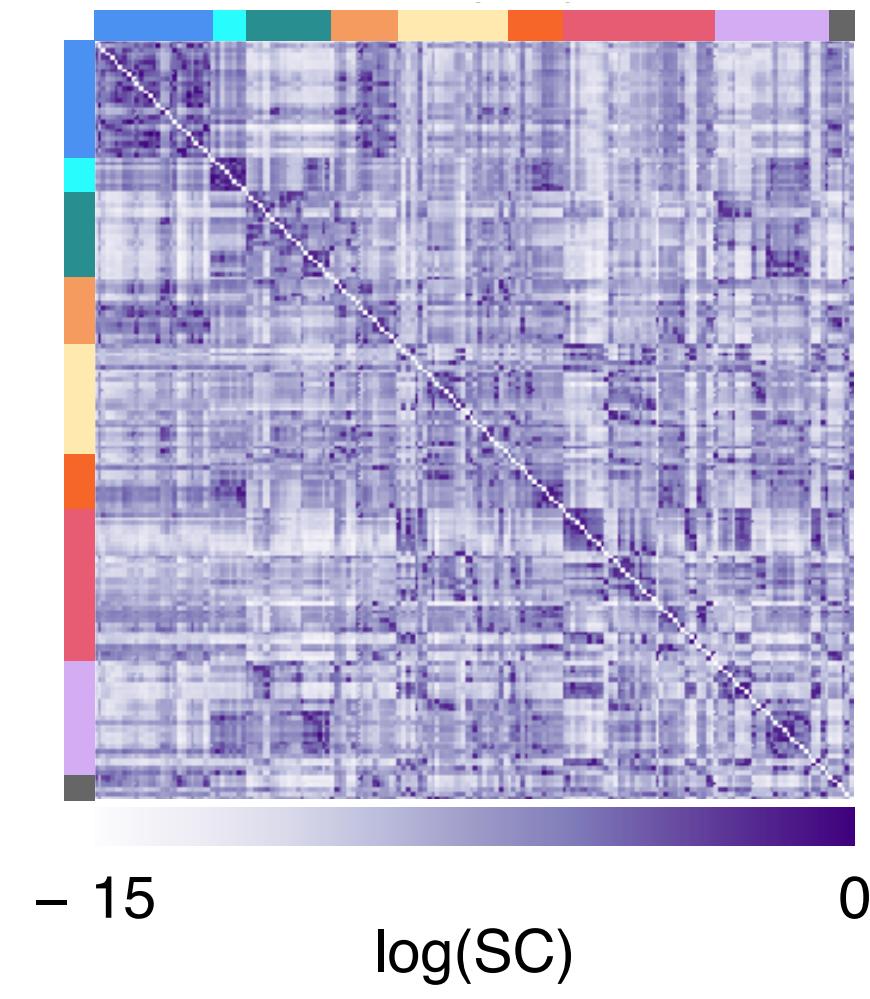
- ▶ Cortical gene expression variation is dominated by a single principal axis which is highly correlated with the T1w/T2w map
- ▶ Hierarchical gradients of microscale properties may contribute to sensory–association specialization of cortical function.



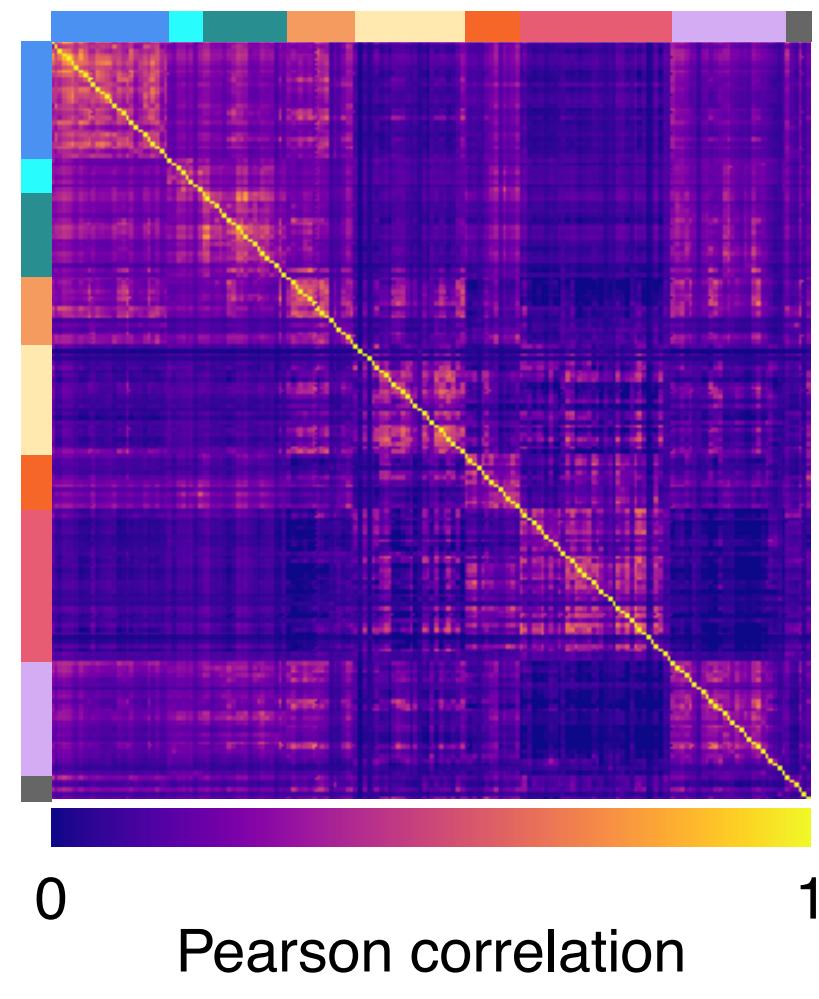
Simulated functional connectivity in large-scale models

Murat Demirtaş

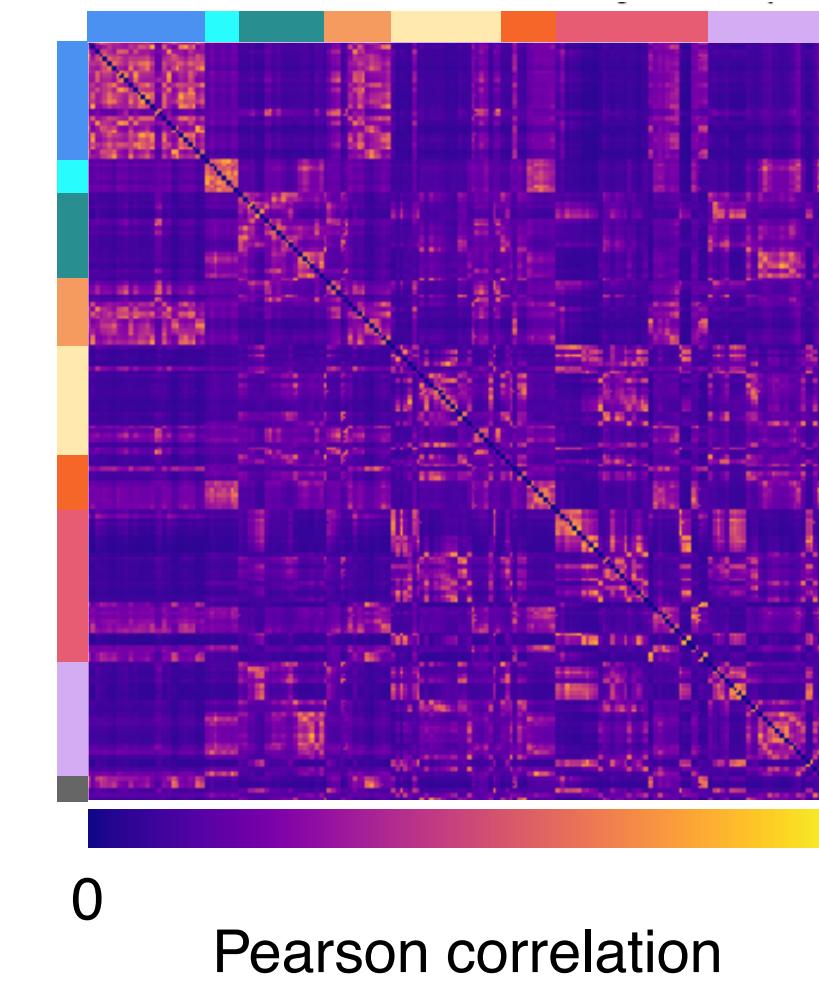
Empirical structural connectivity (SC)



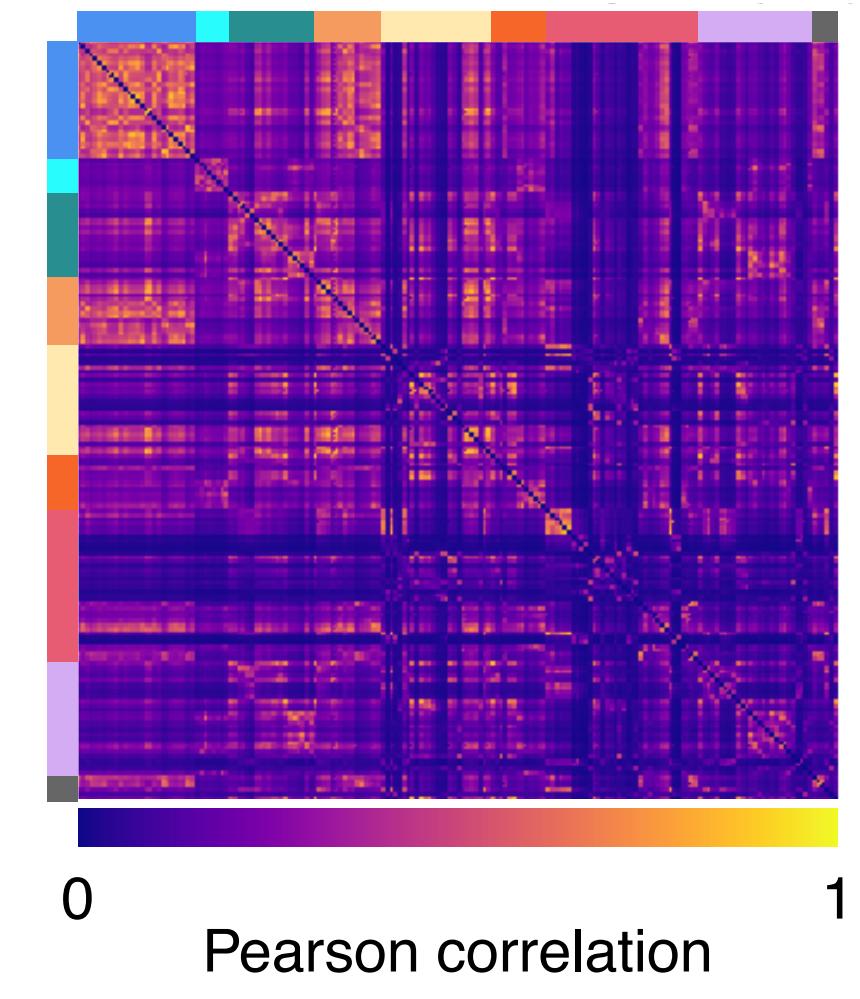
Empirical functional connectivity (FC)



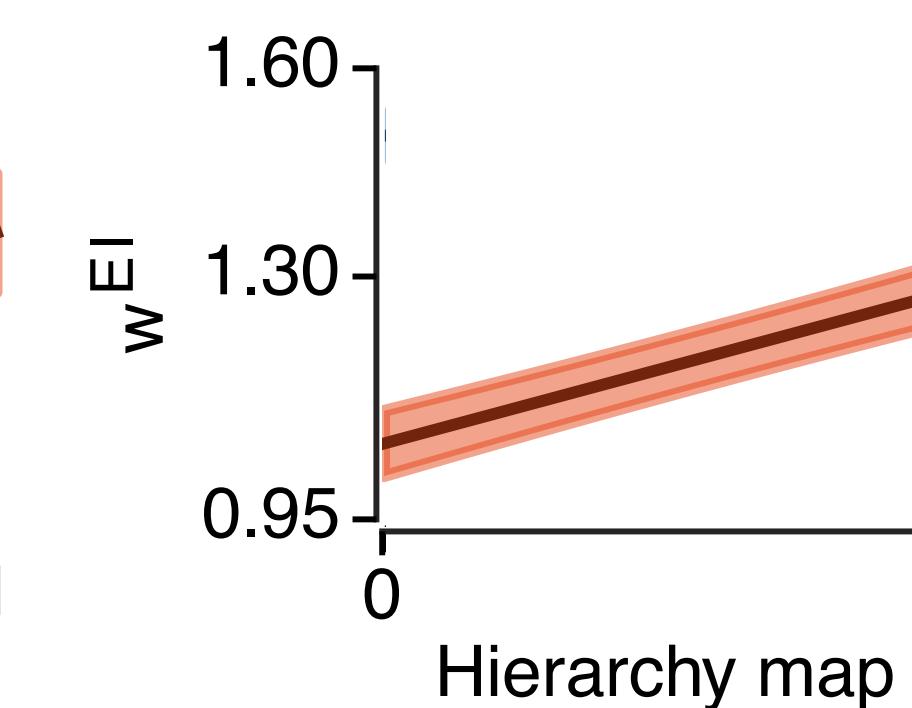
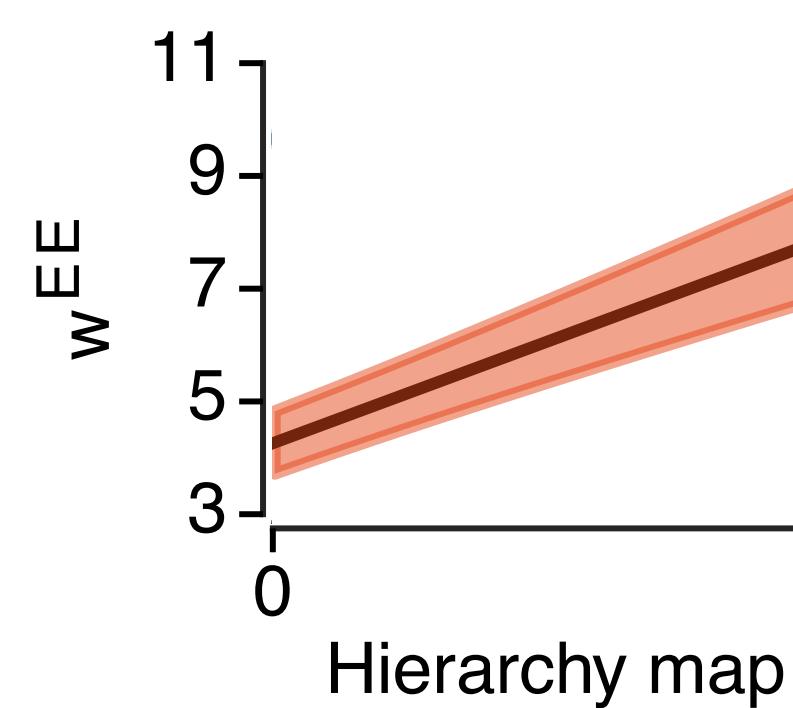
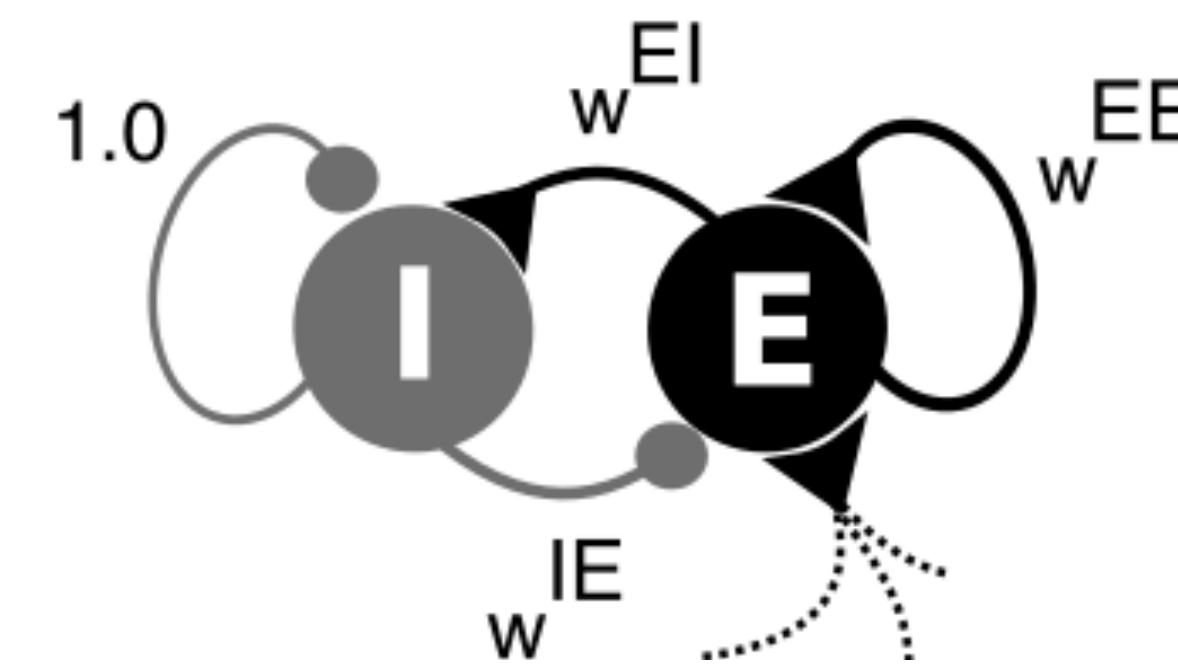
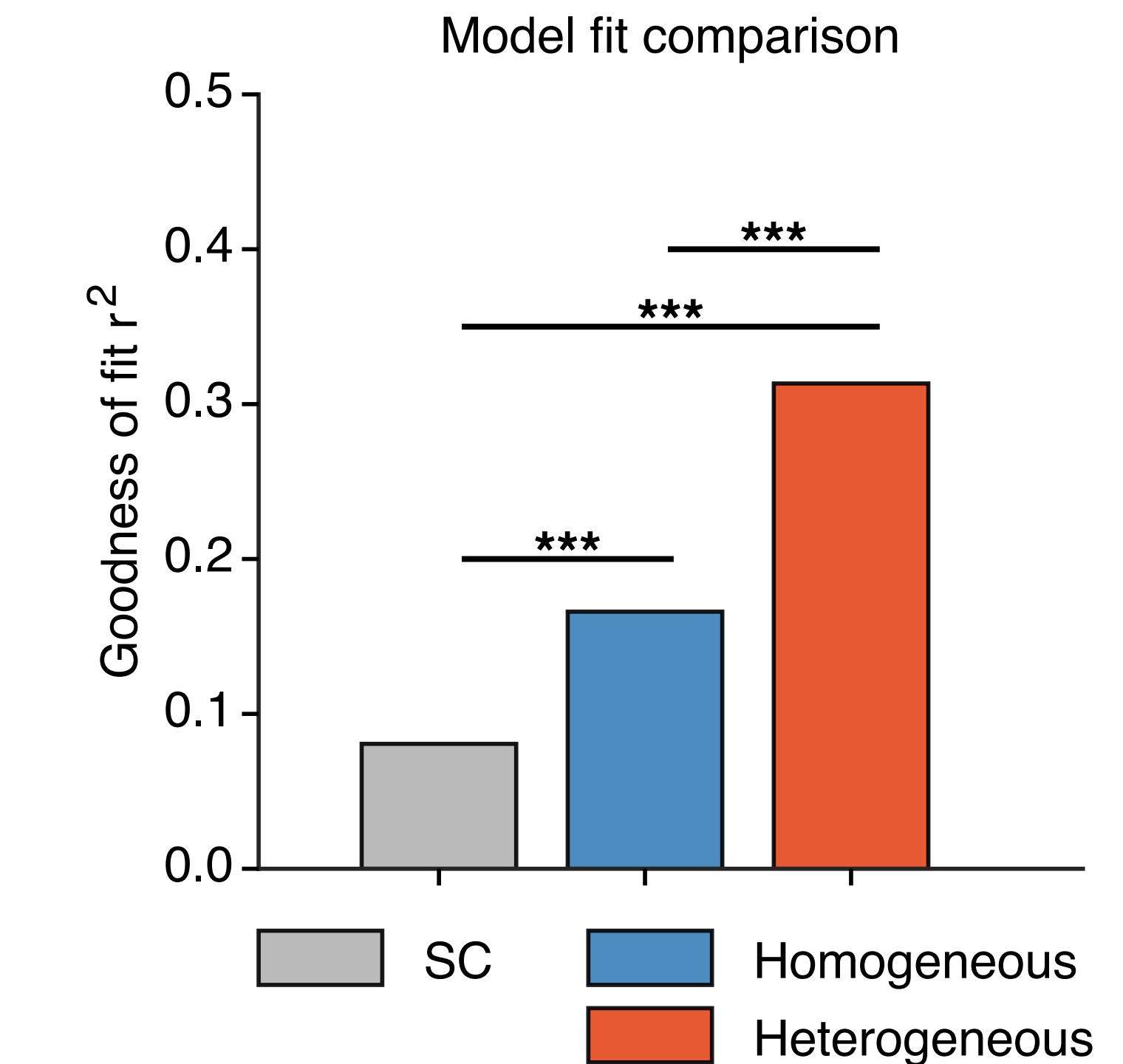
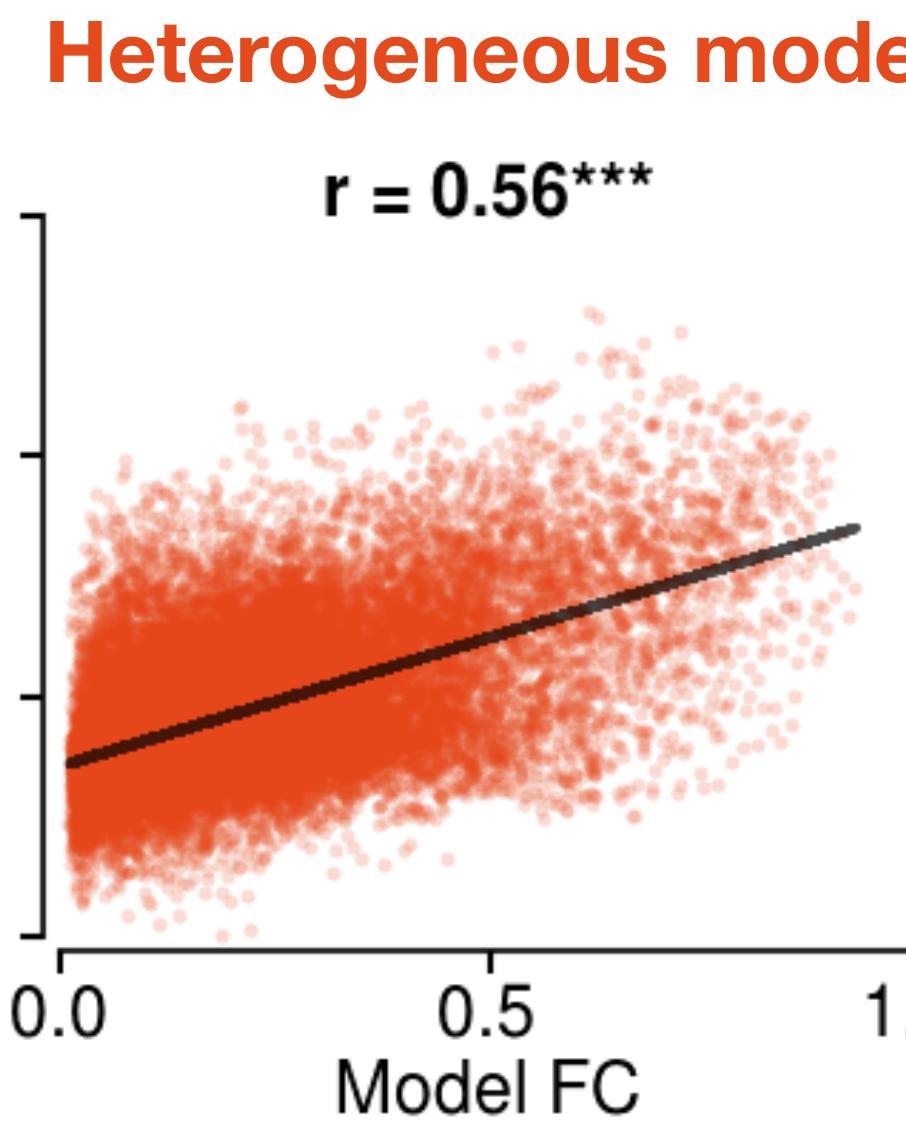
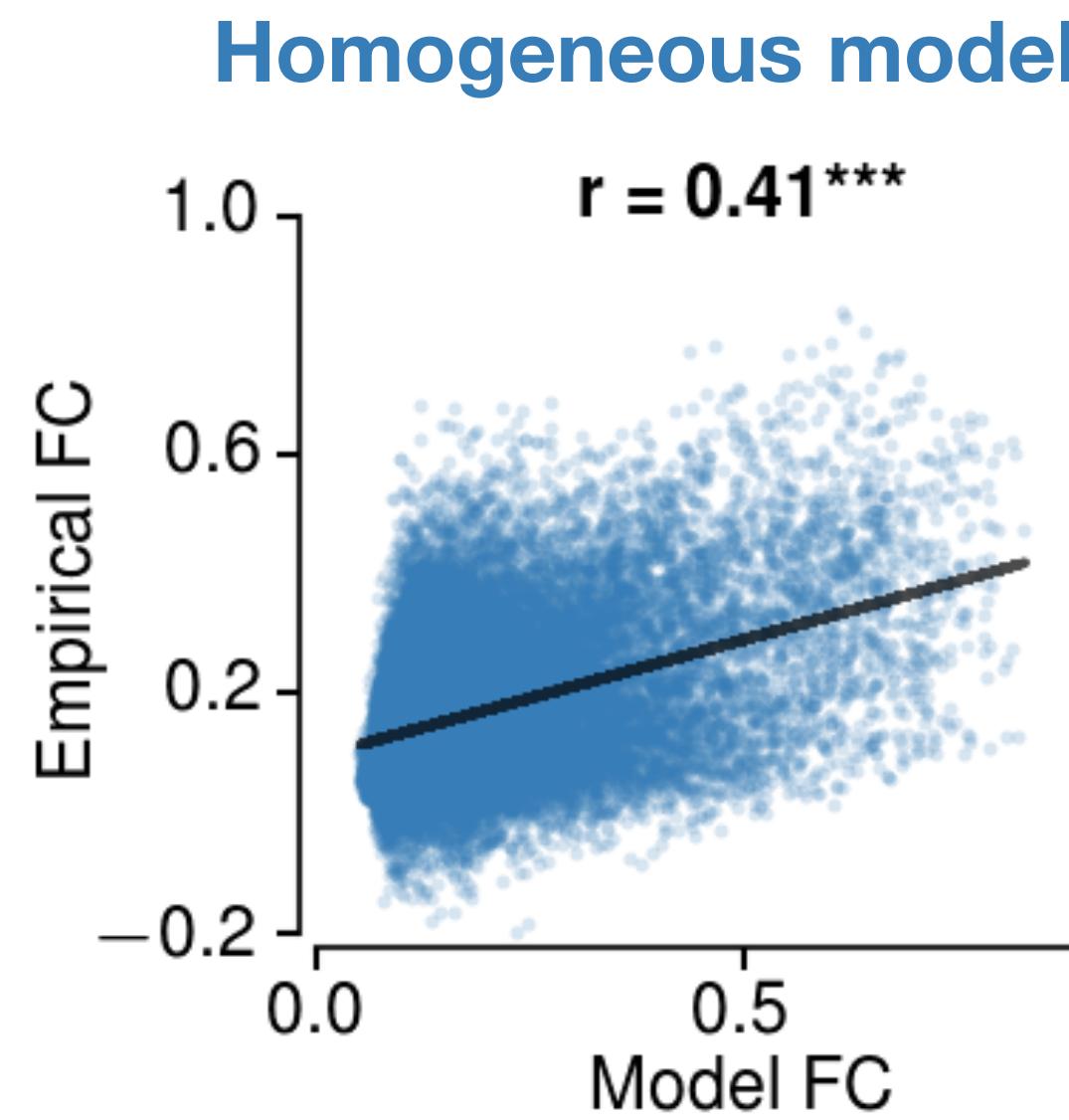
Homogeneous model FC



Heterogeneous model FC



Hierarchical heterogeneity improves model fit to functional connectivity

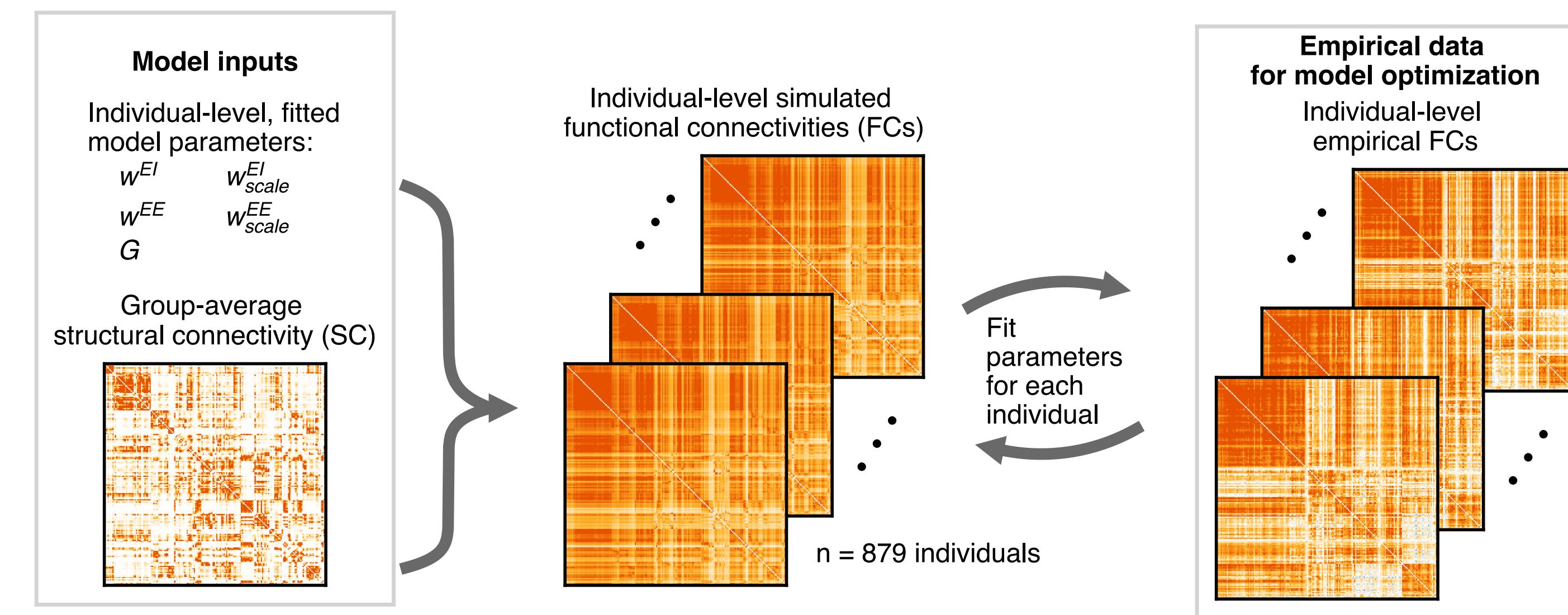
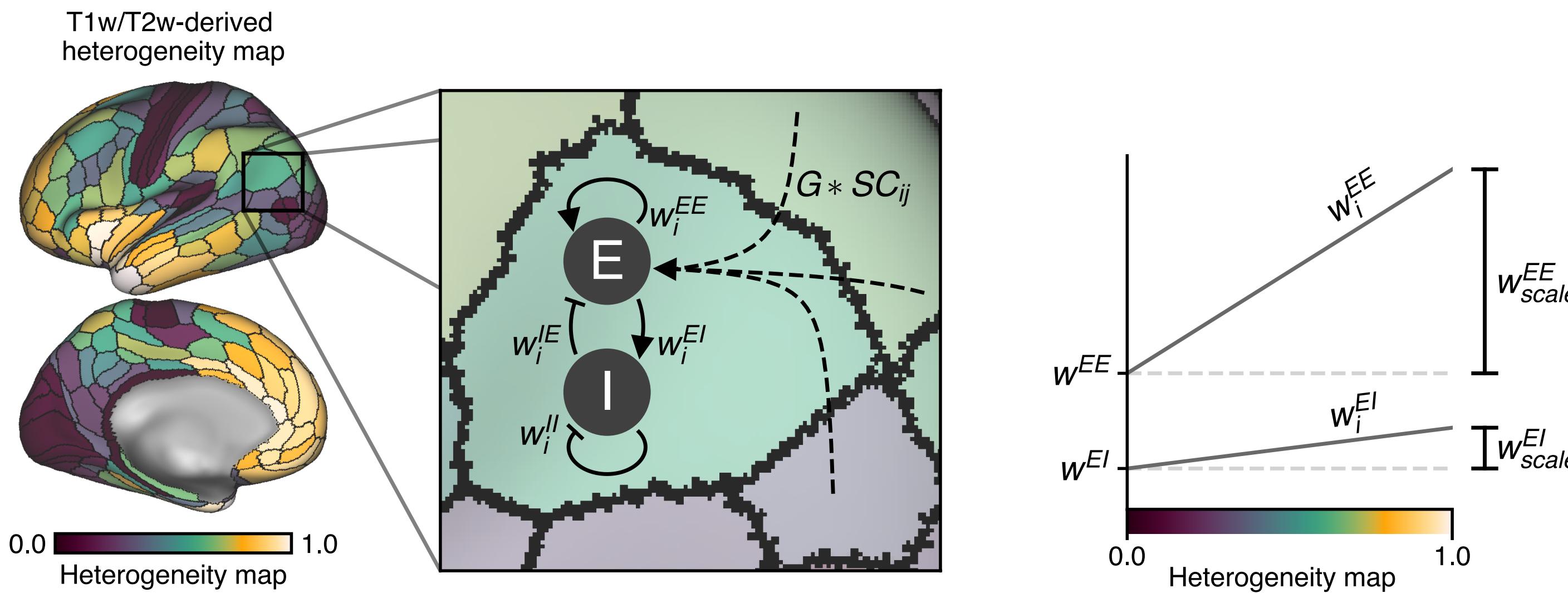


Increasing local
recurrent strength
along cortical
hierarchy

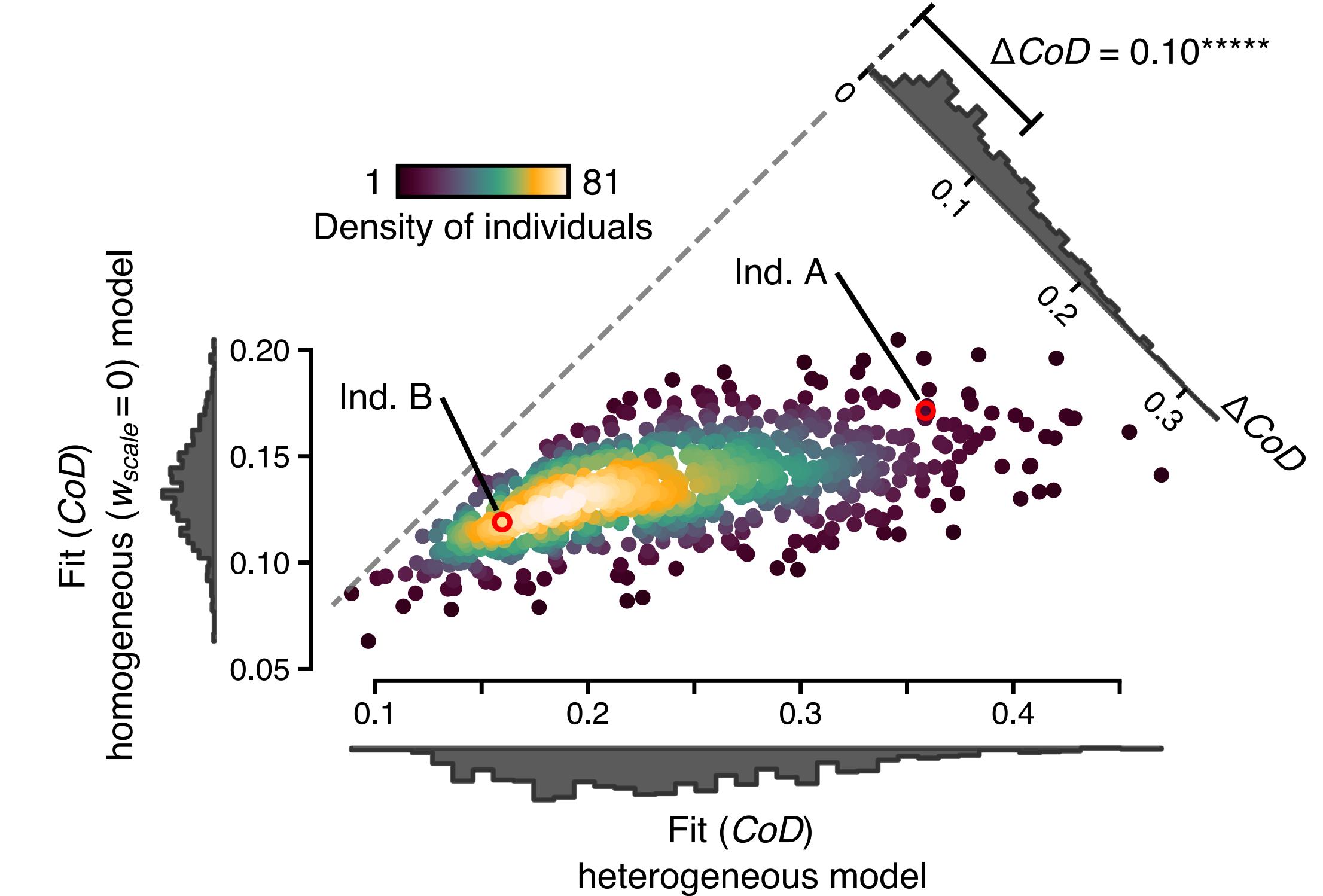
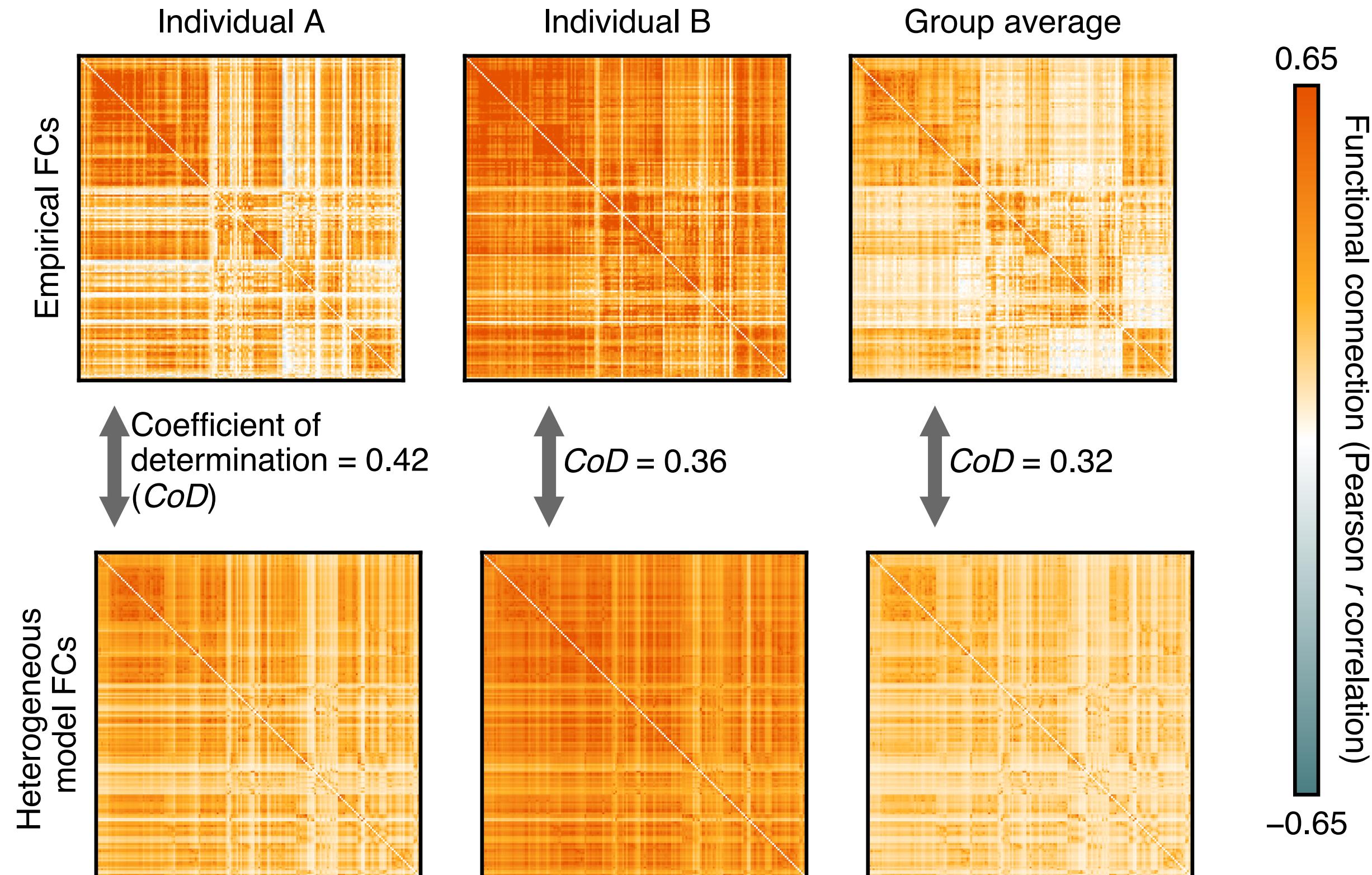


Individual-subject modeling of functional connectivity

Rachel Cooper

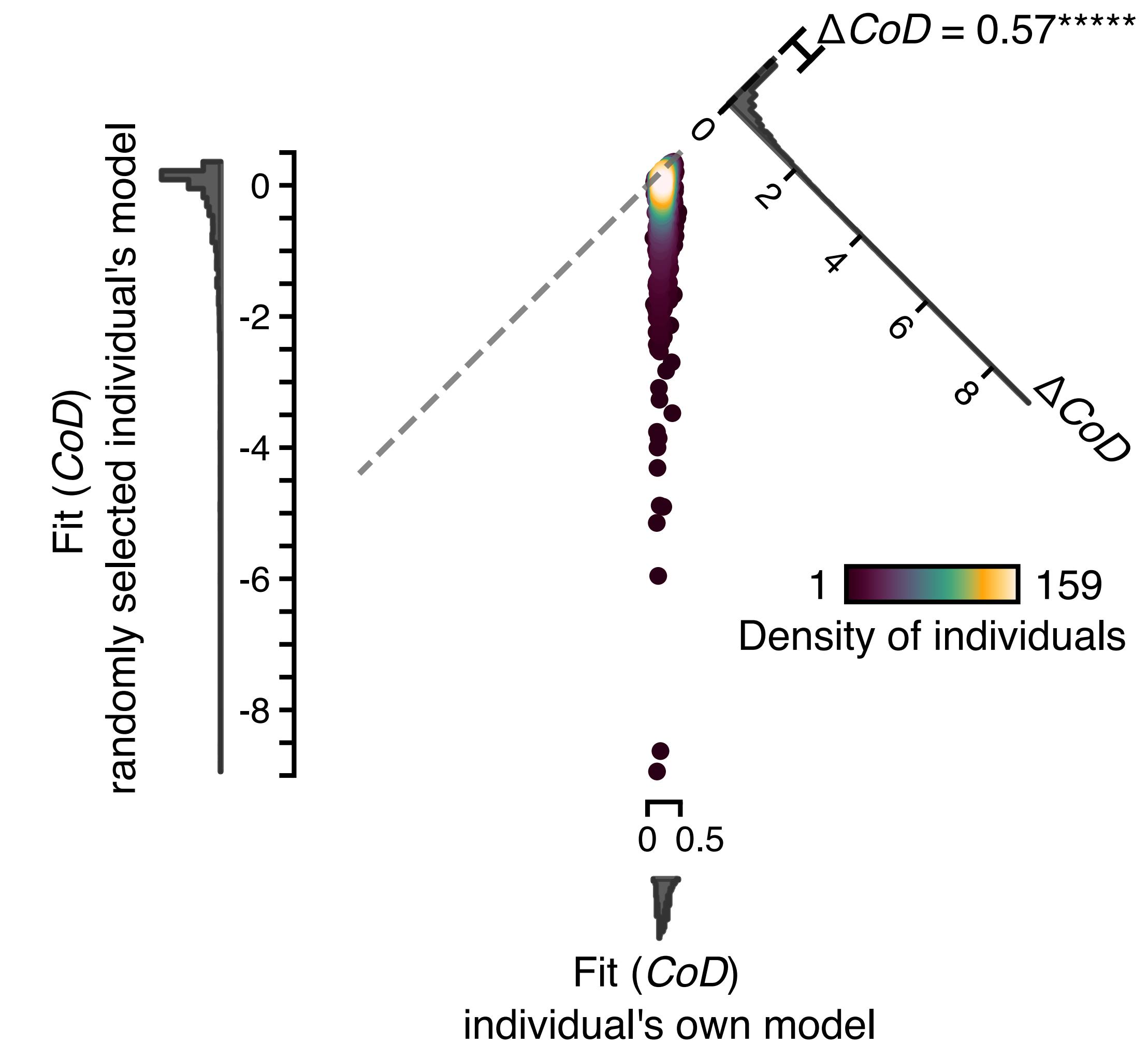
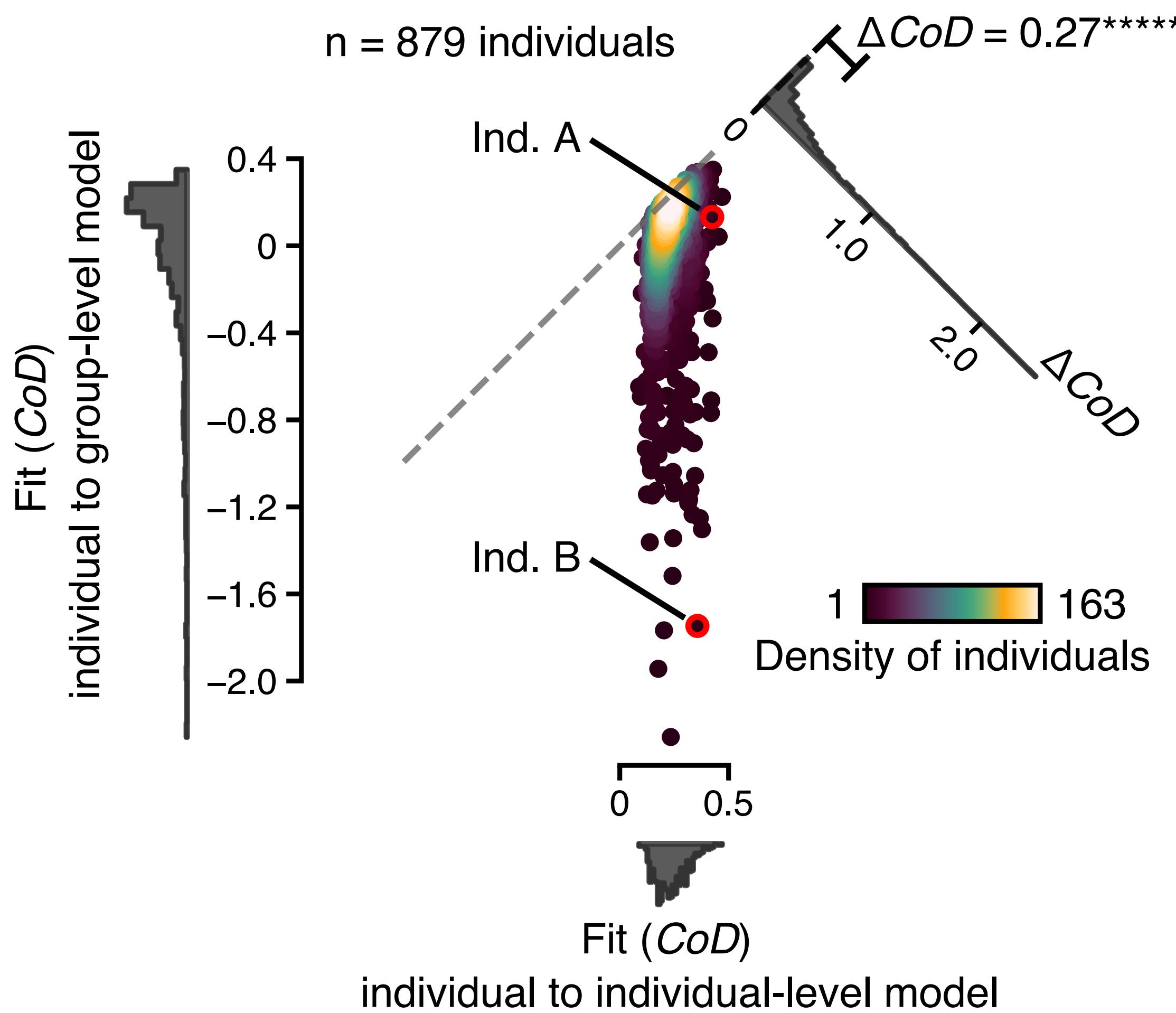


Individual-subject modeling of functional connectivity

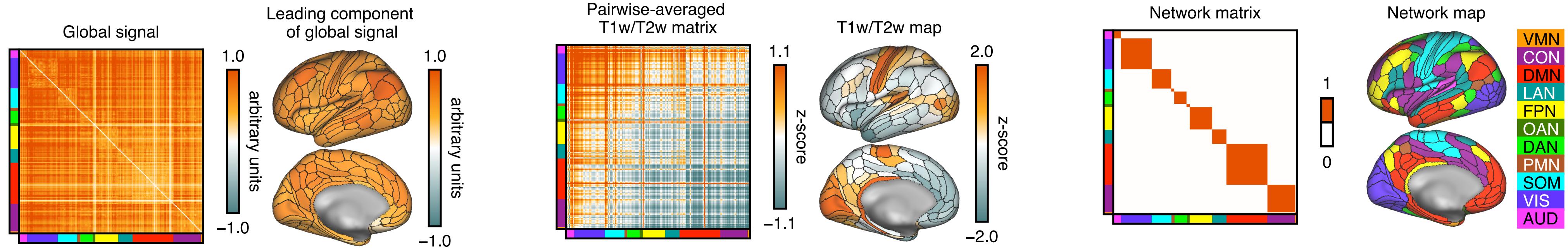
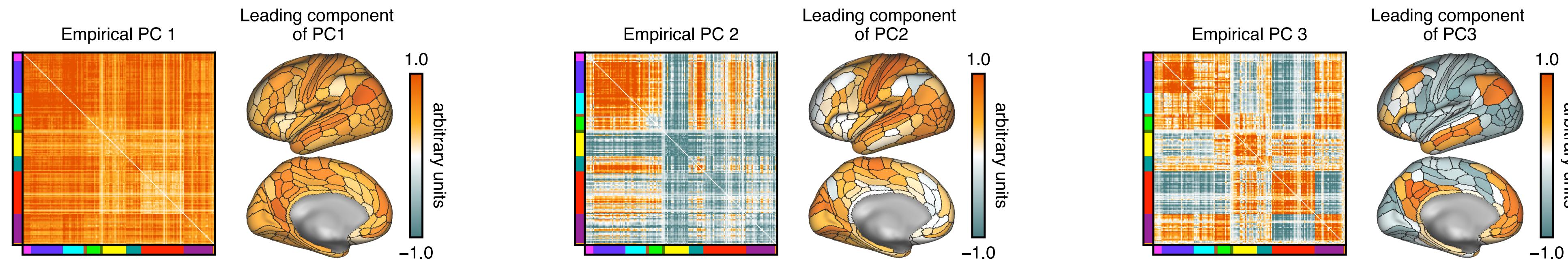
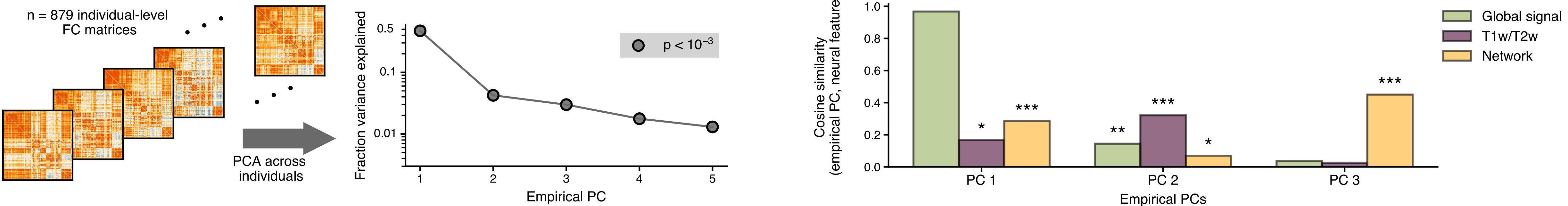


Fit measure: Coefficient of Determination (COD) = $1 - \frac{MSE(\text{predicted, observed})}{MSE(\text{predicted}, \hat{\mu})}$

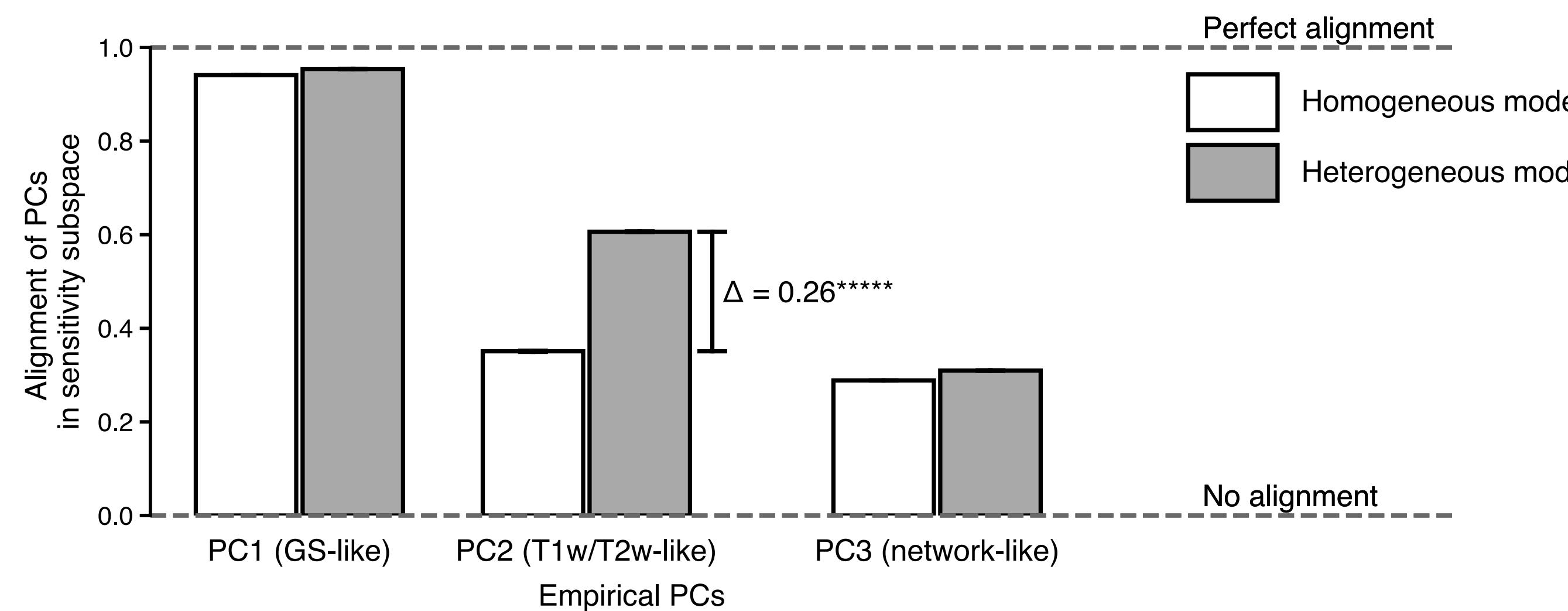
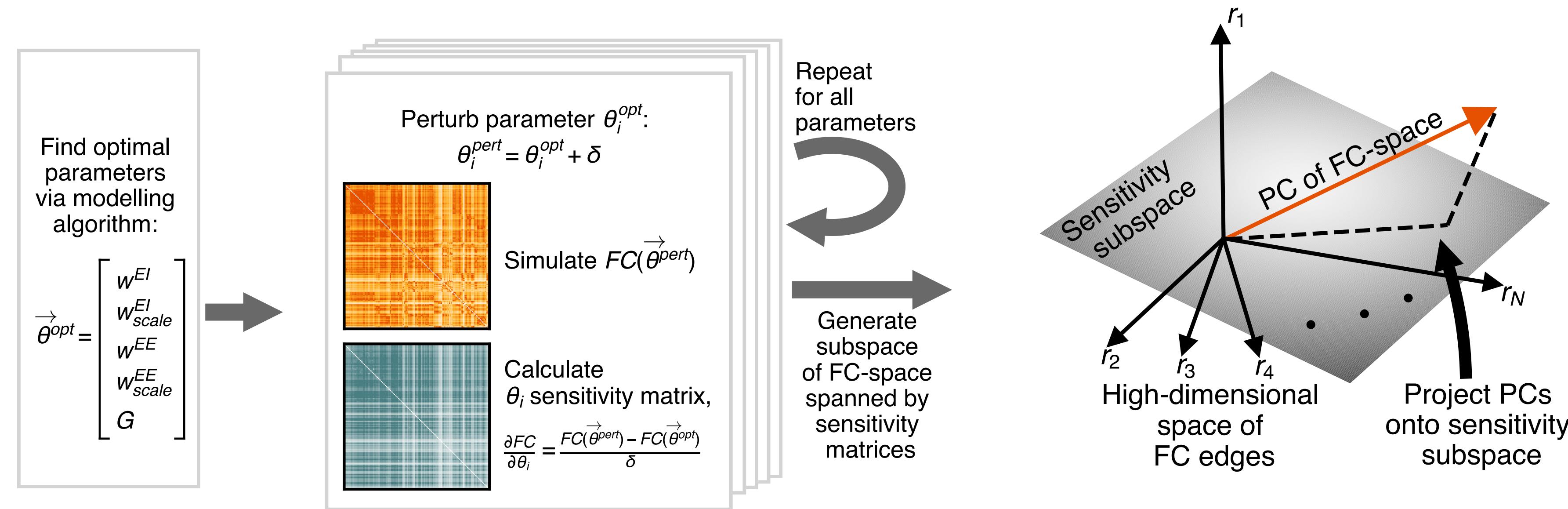
Individual-subject modeling of functional connectivity



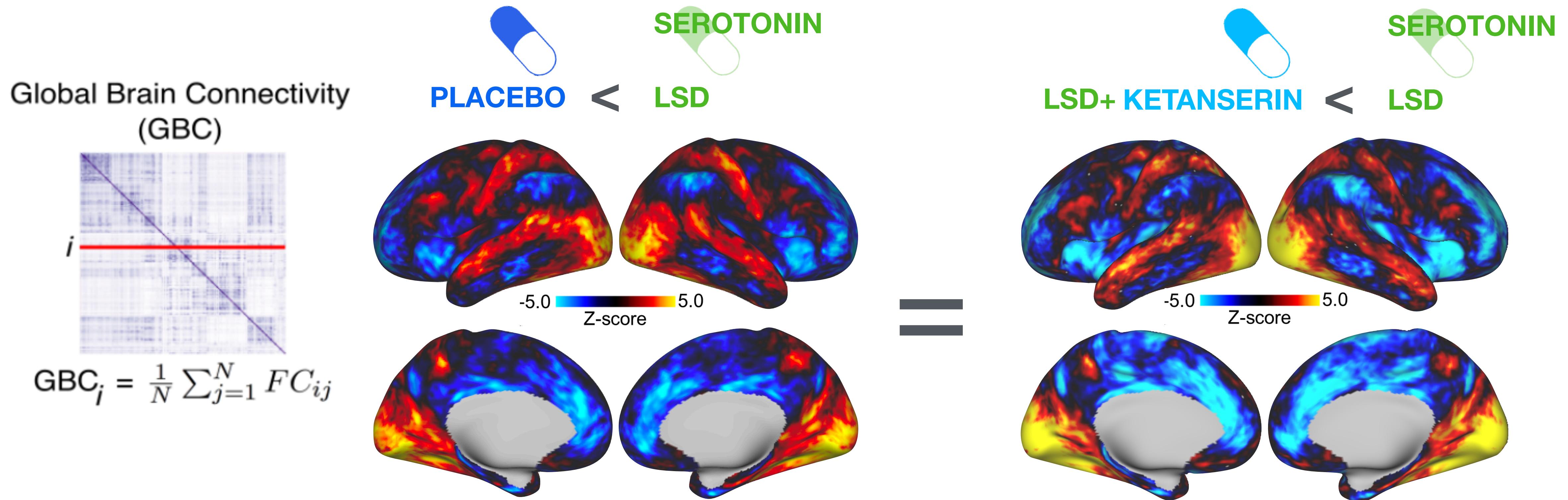
Modes of population variation



Model expressivity to capture modes of population variation



LSD effects on resting-state functional connectivity

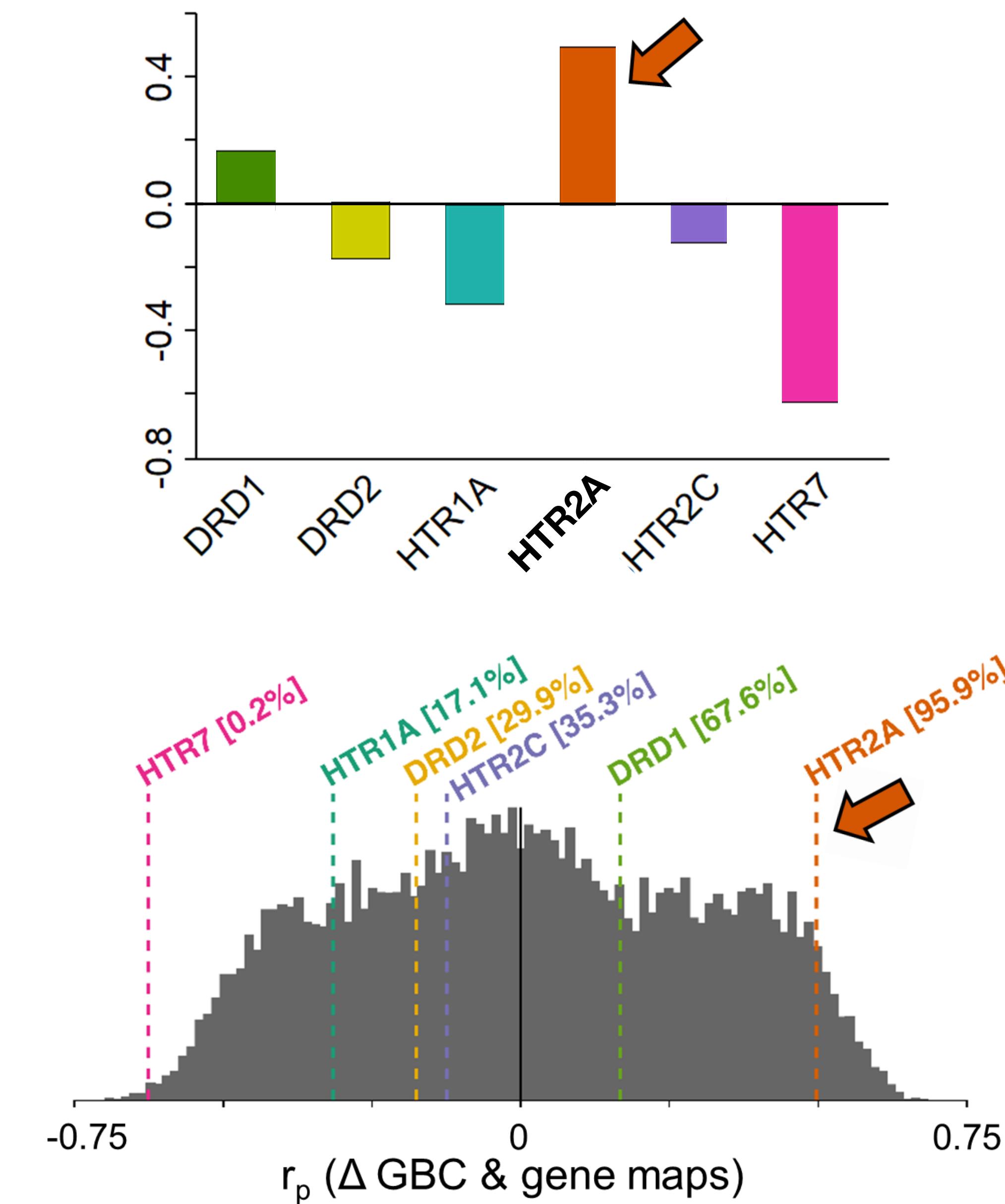
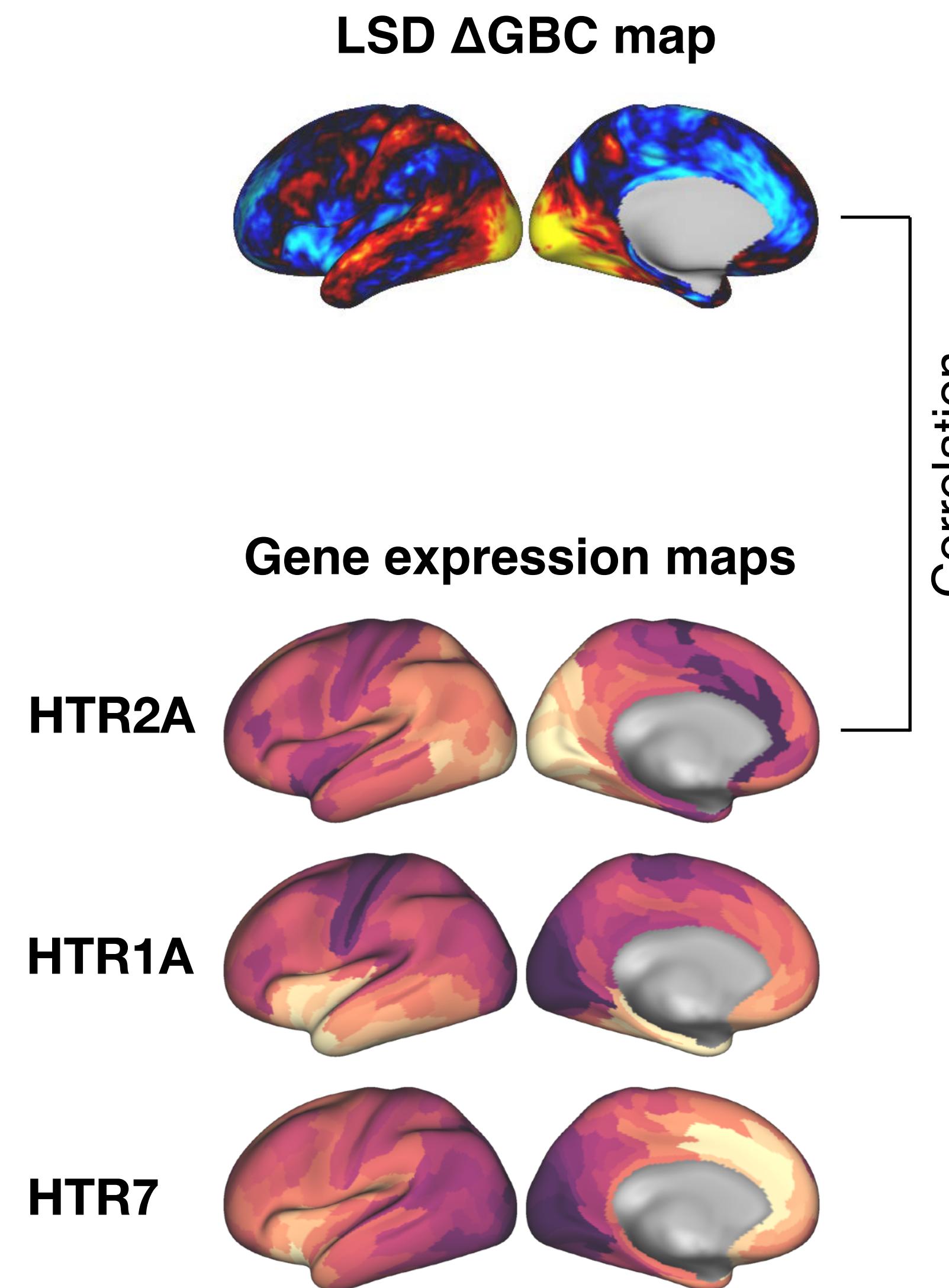


- ▶ Neural and behavioral effects of LSD blocked by ketanserin, a selective antagonist of the serotonergic **5-HT2A** receptor
- ▶ Hypothesis: map aligns with expression of gene **HTR2A**

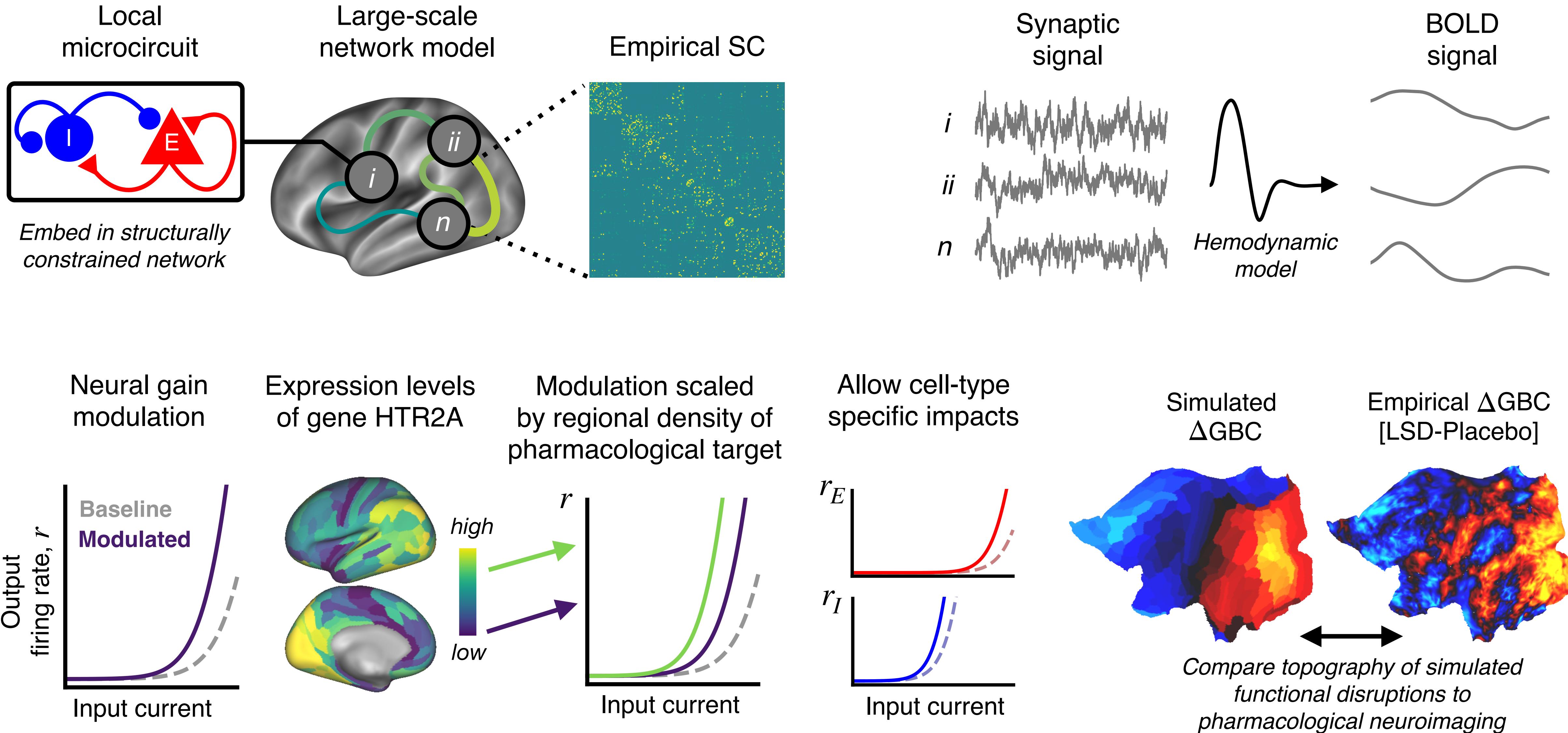
Identifying molecular candidates of neuroimaging effects



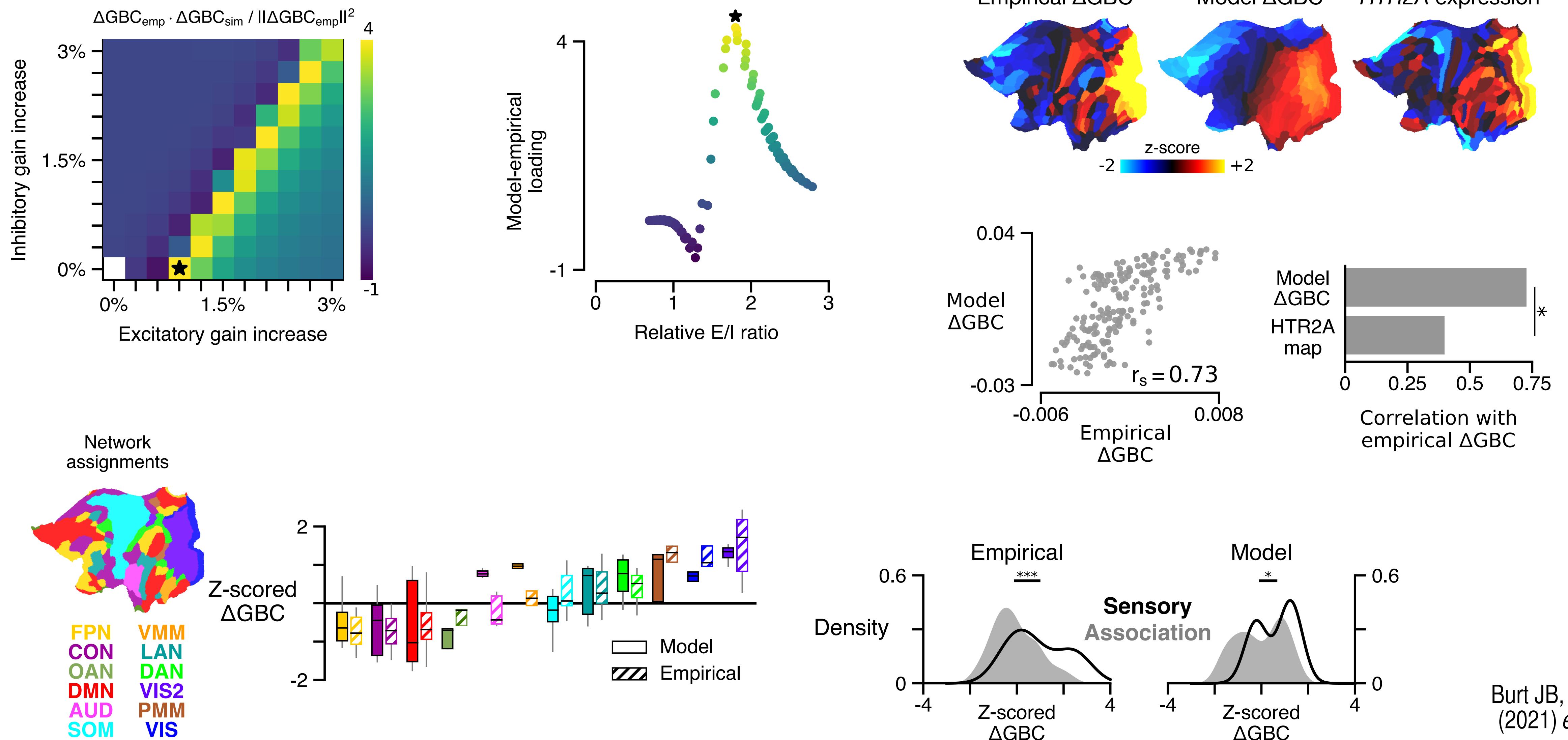
Josh Burt



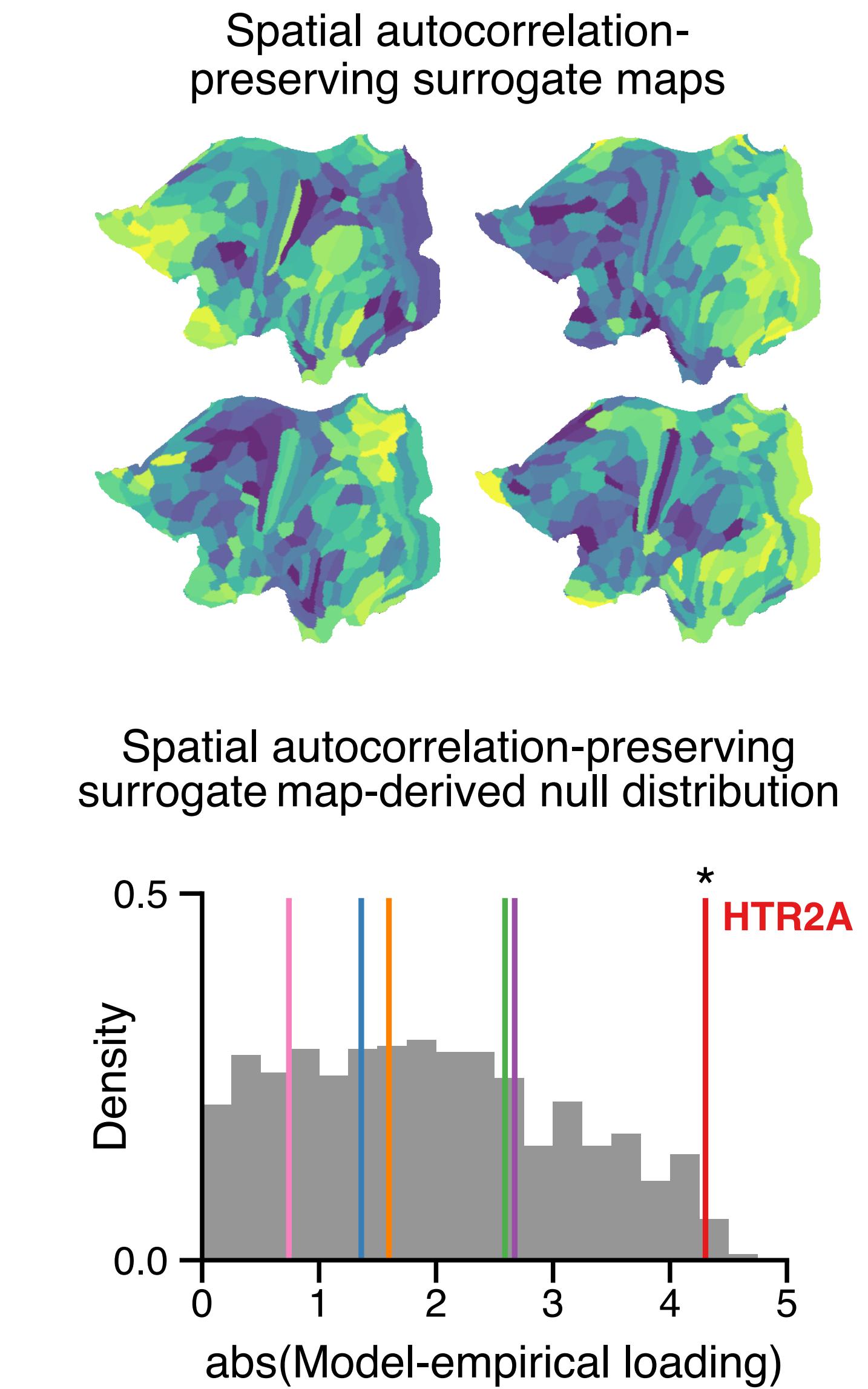
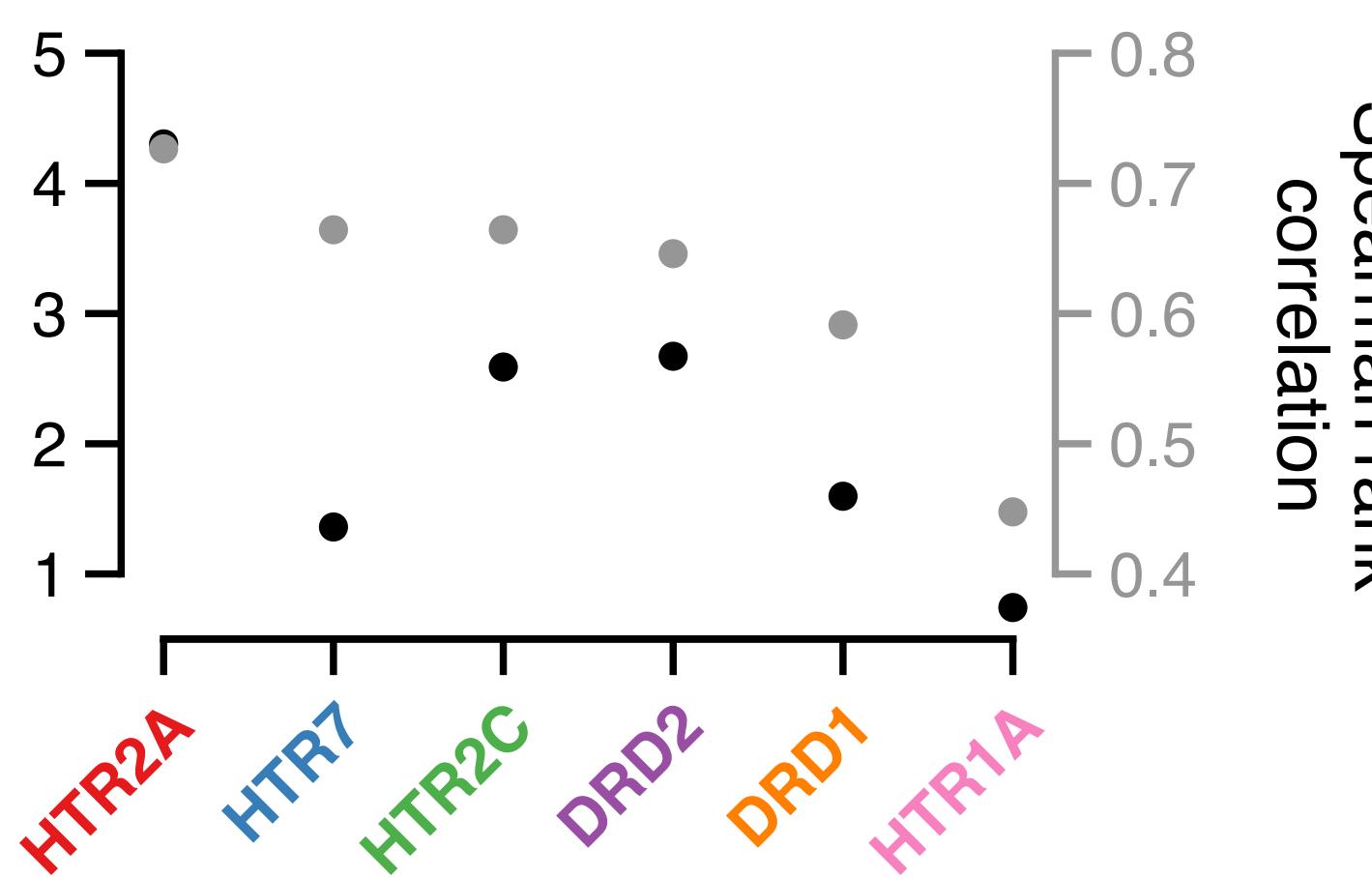
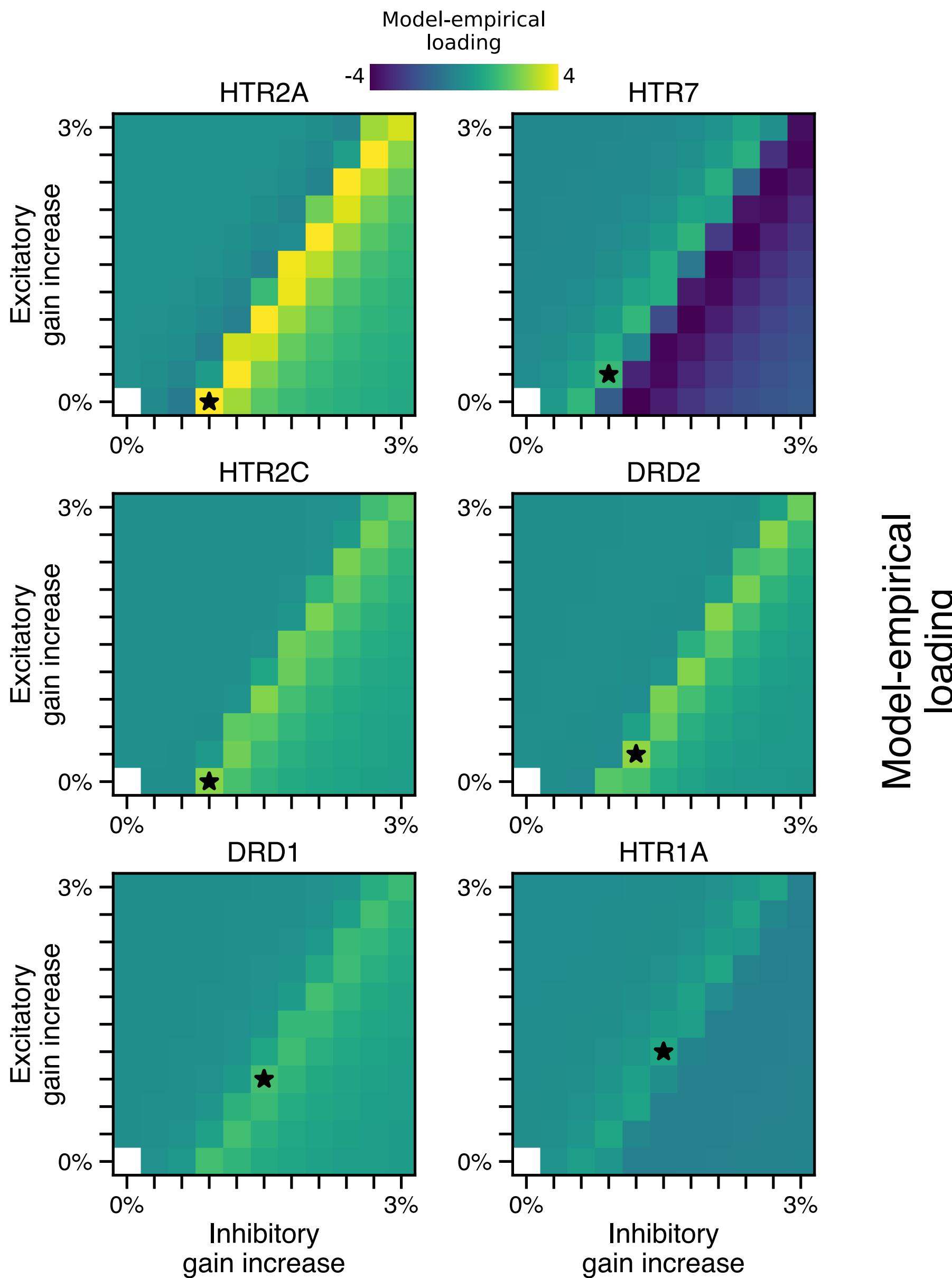
Modeling pharmacological neuroimaging



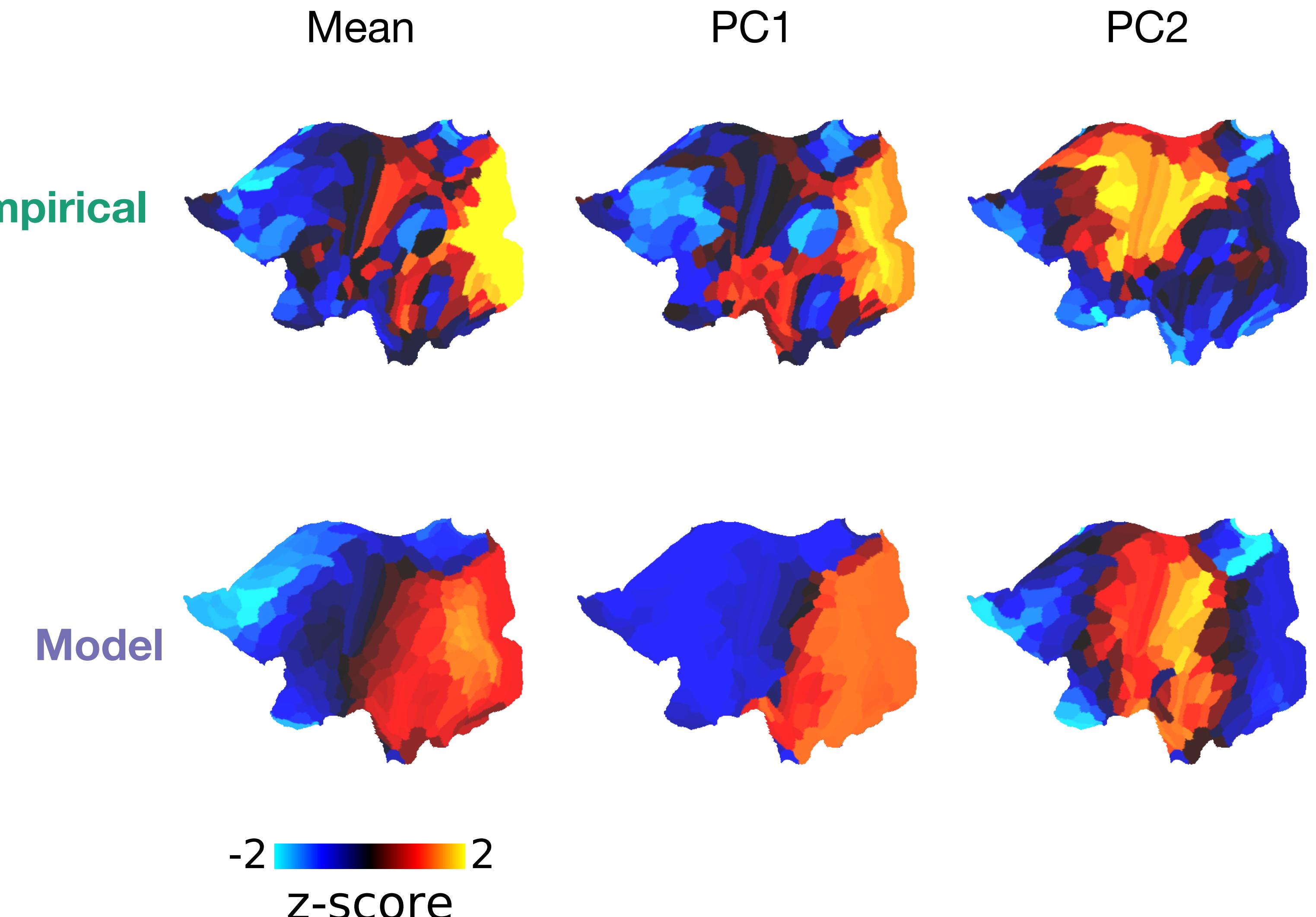
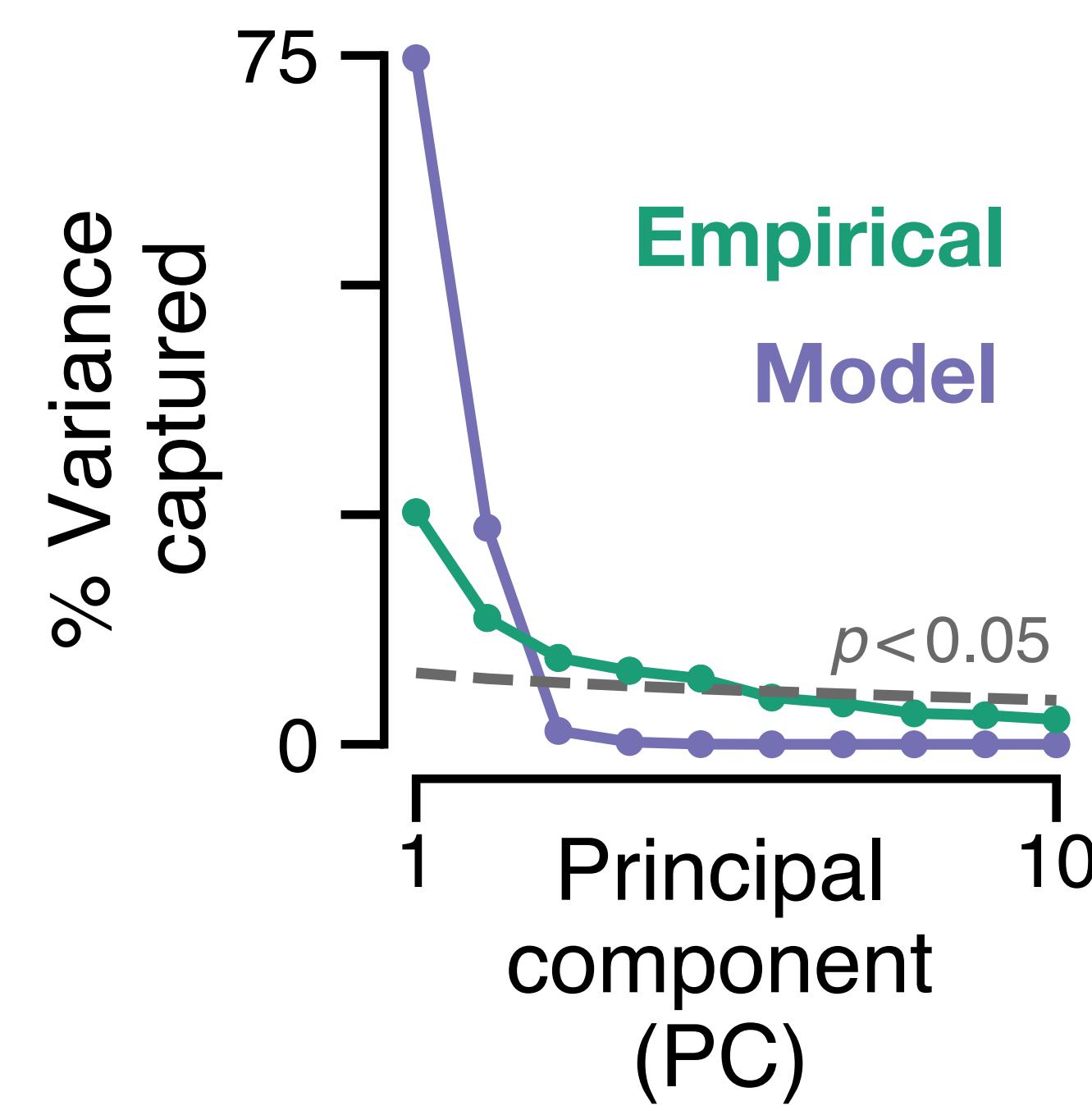
Model captures topography of LSD-induced connectivity changes via HTR2A-mediated gain modulation



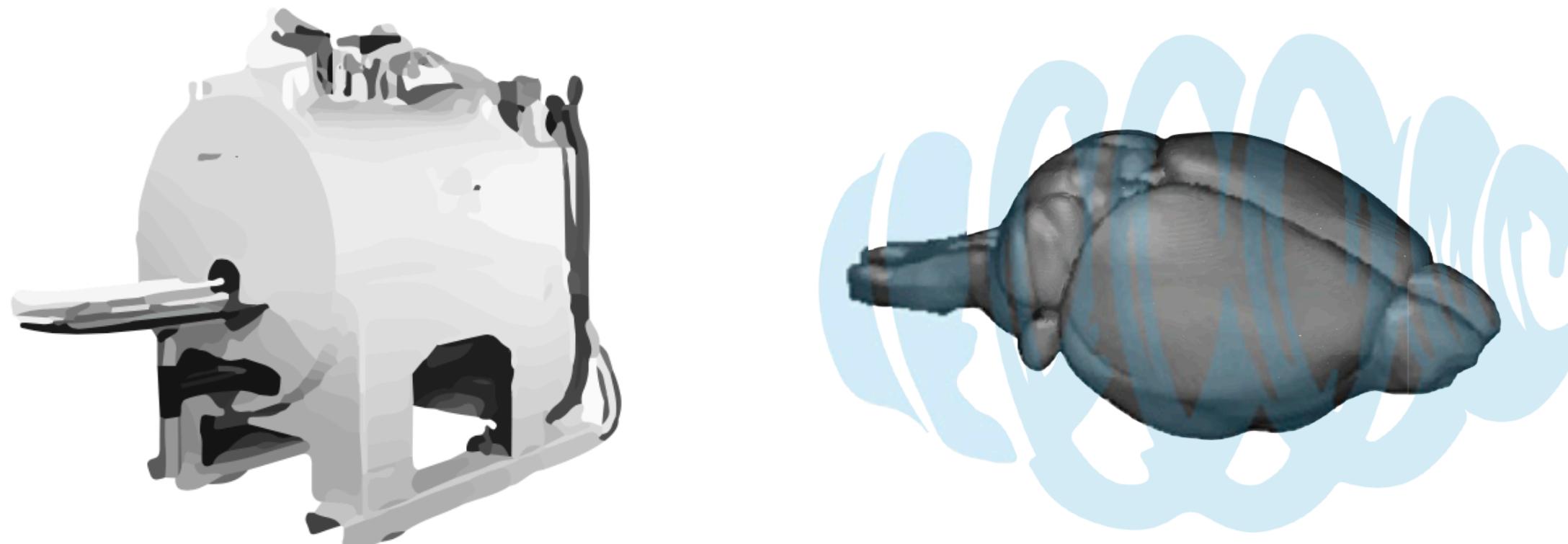
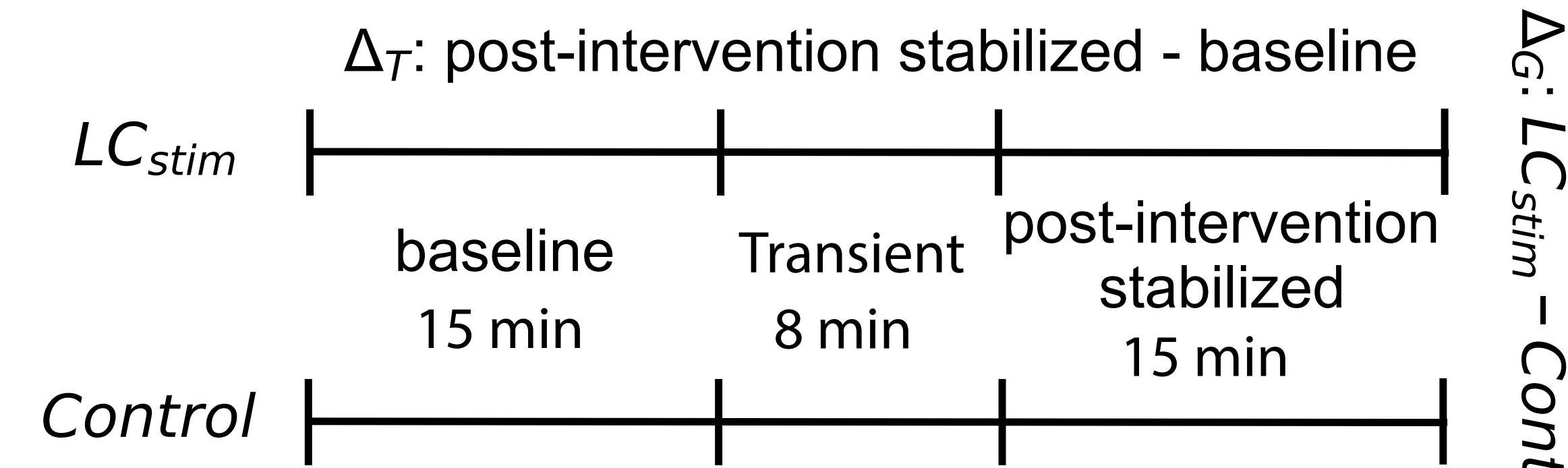
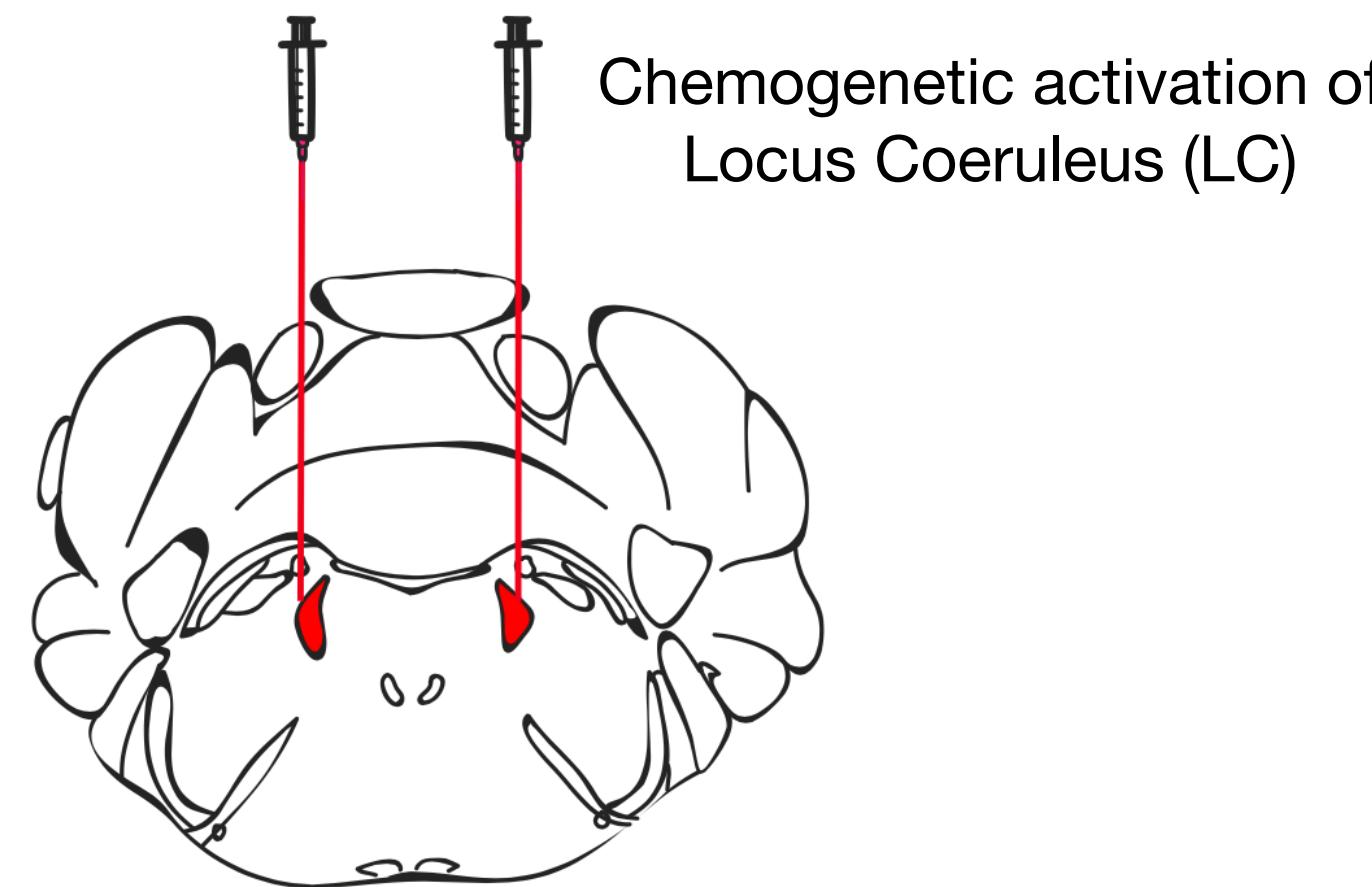
Comparison of HTR2A to alternative gain modulation maps



Individual variation in pharmacological fMRI response



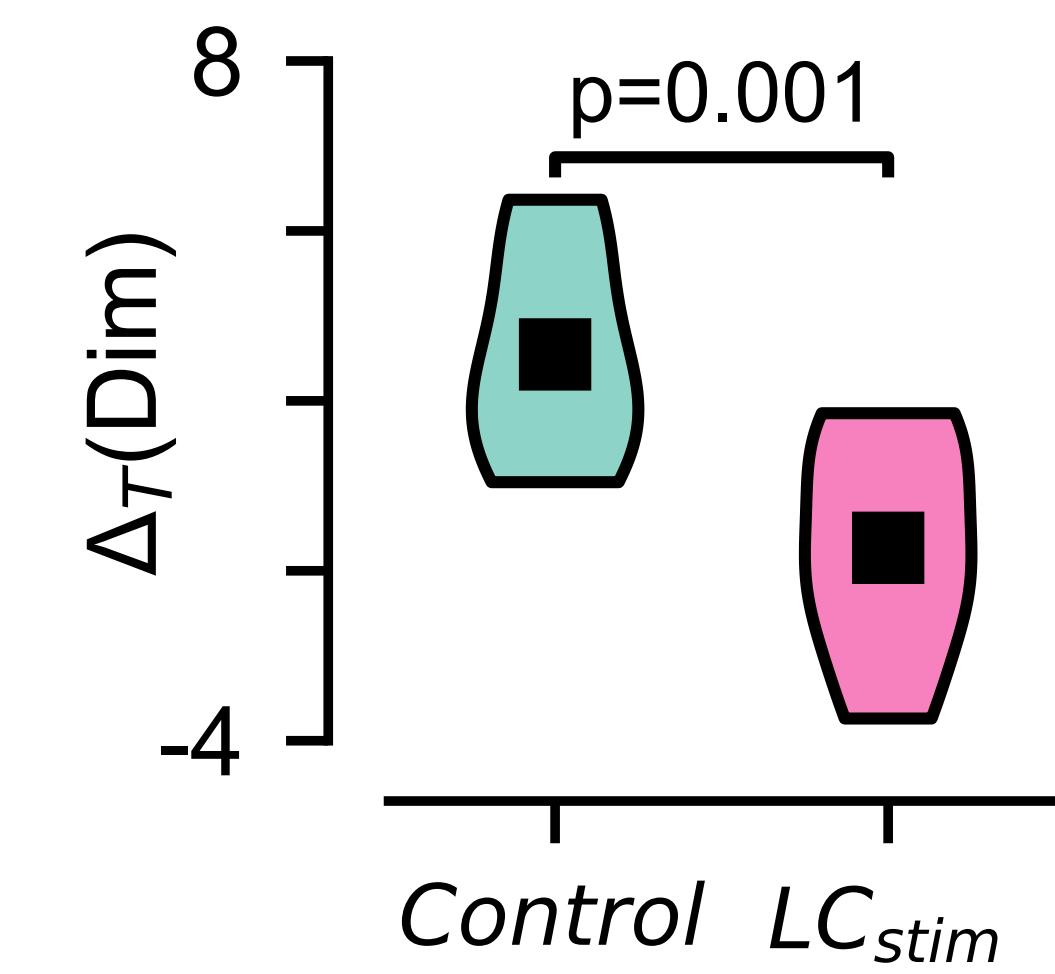
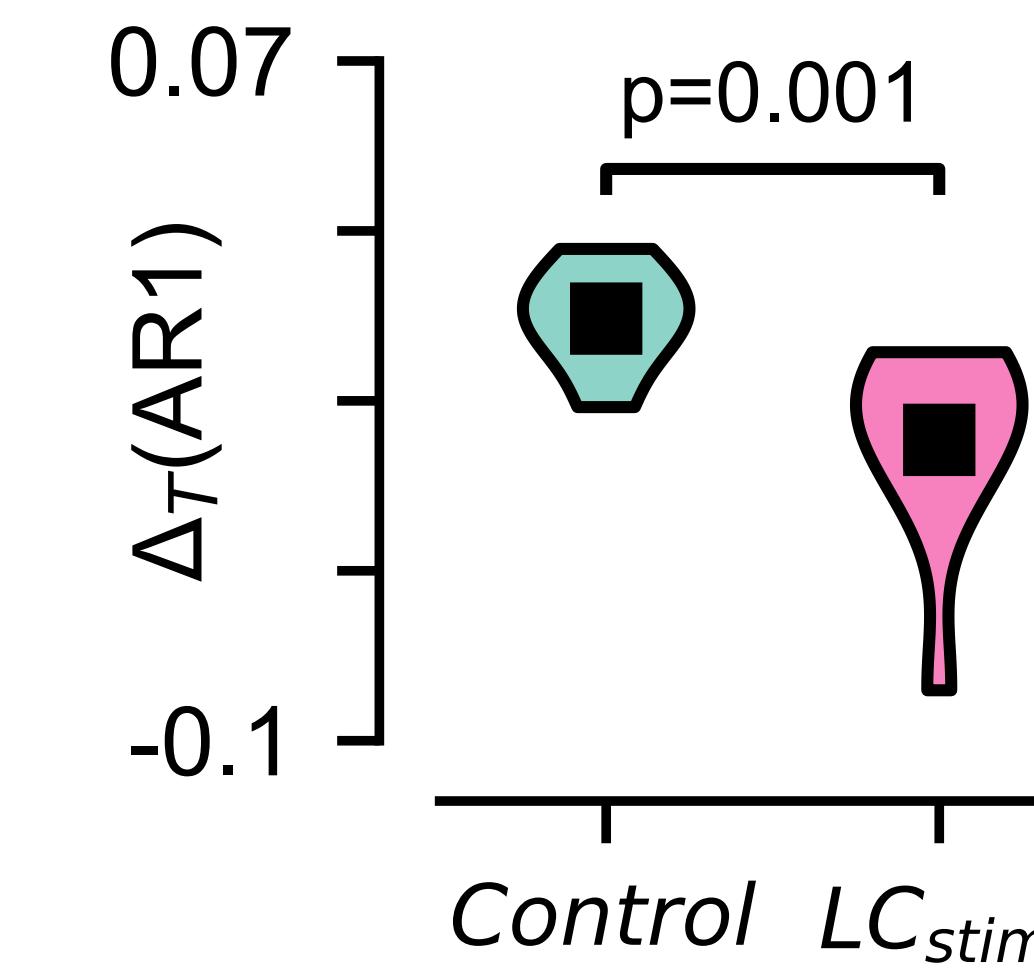
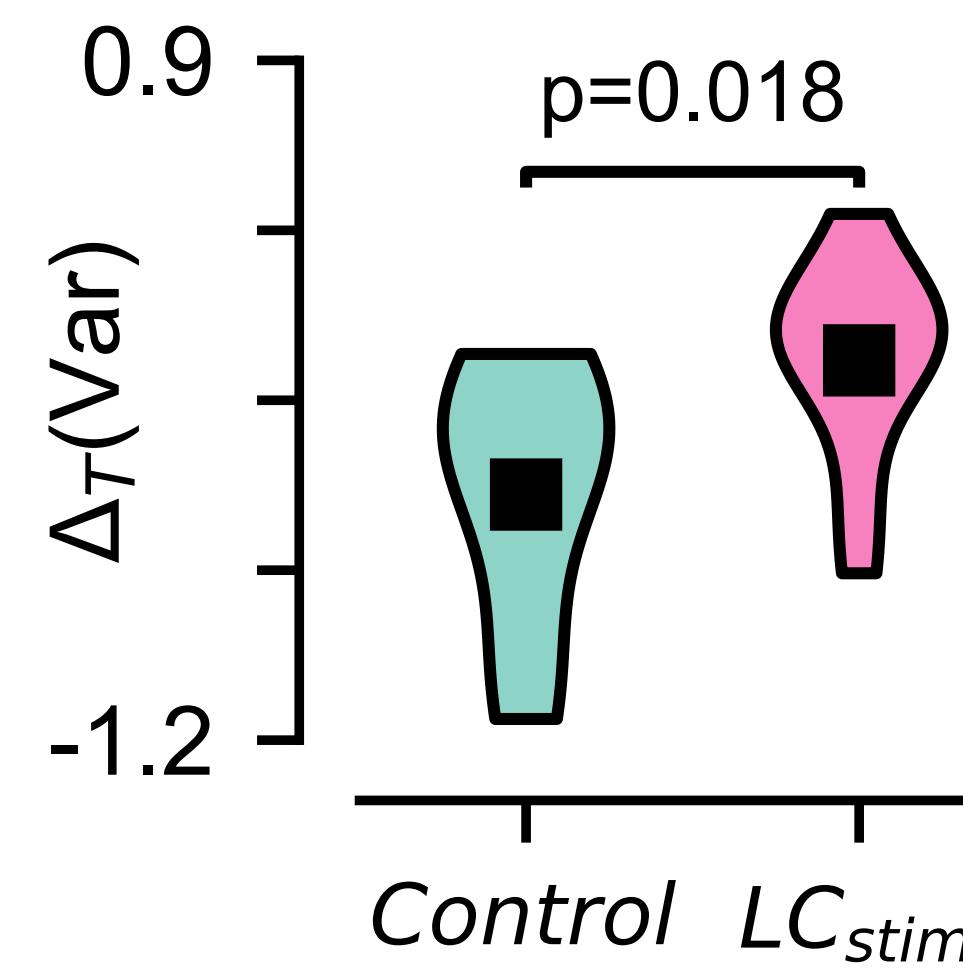
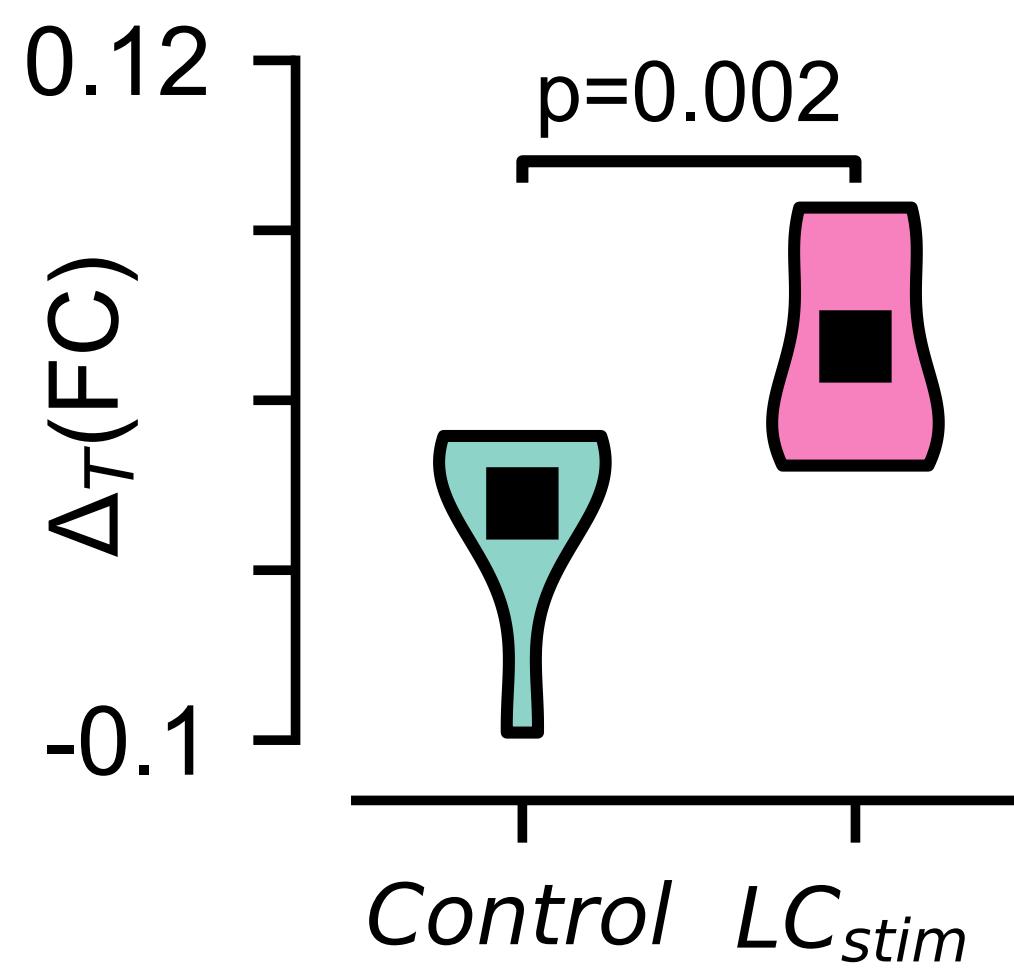
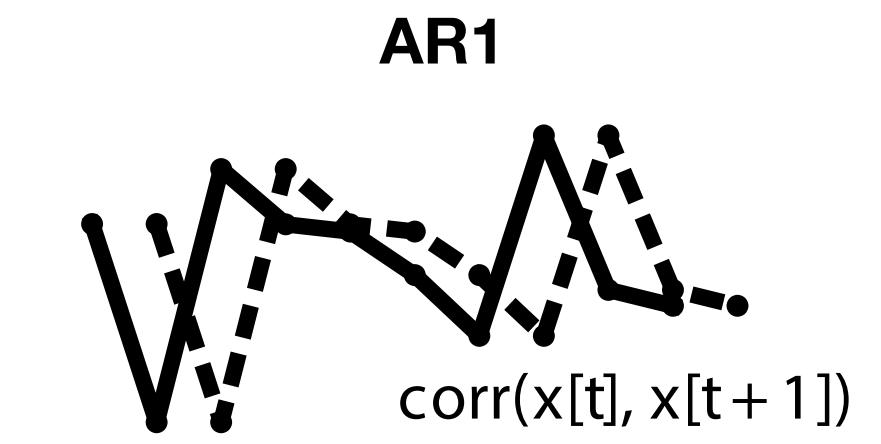
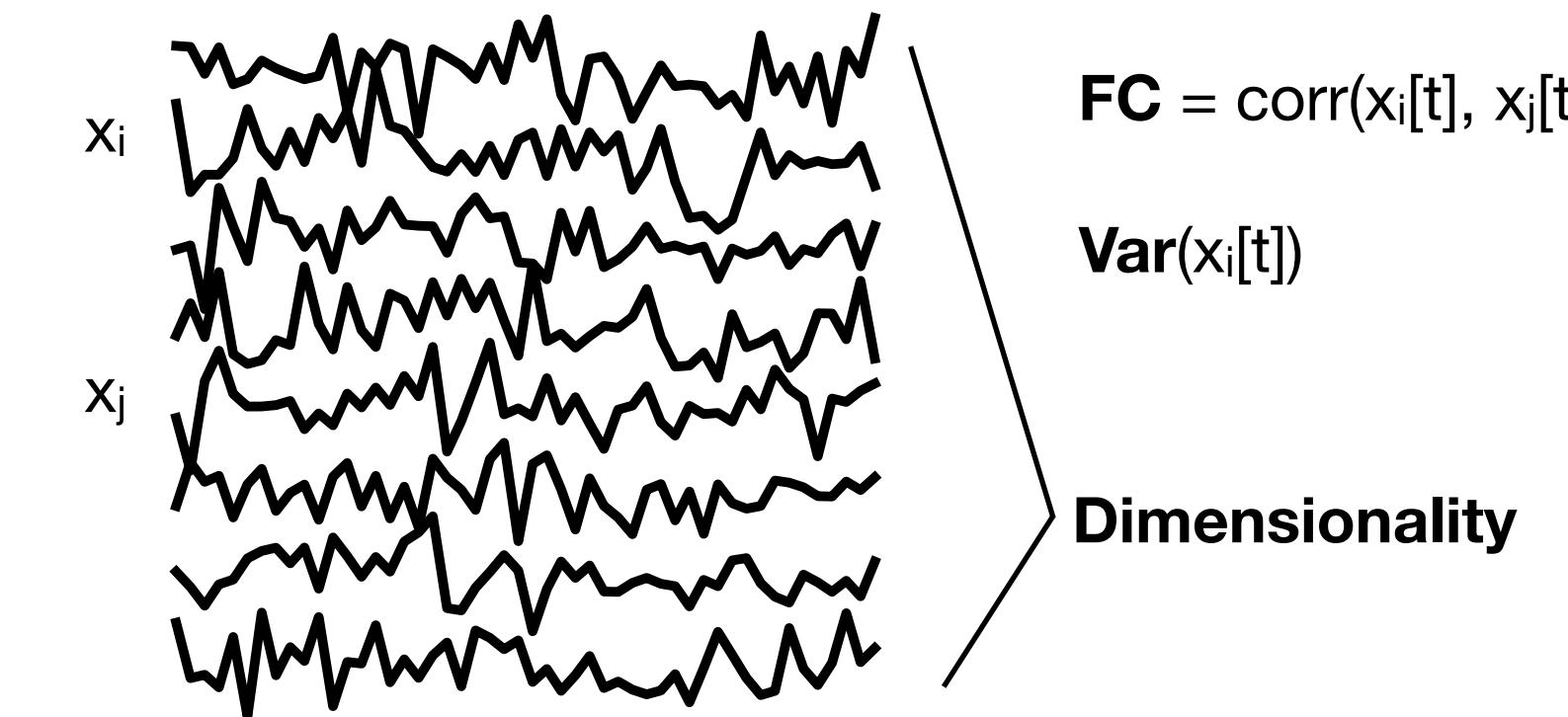
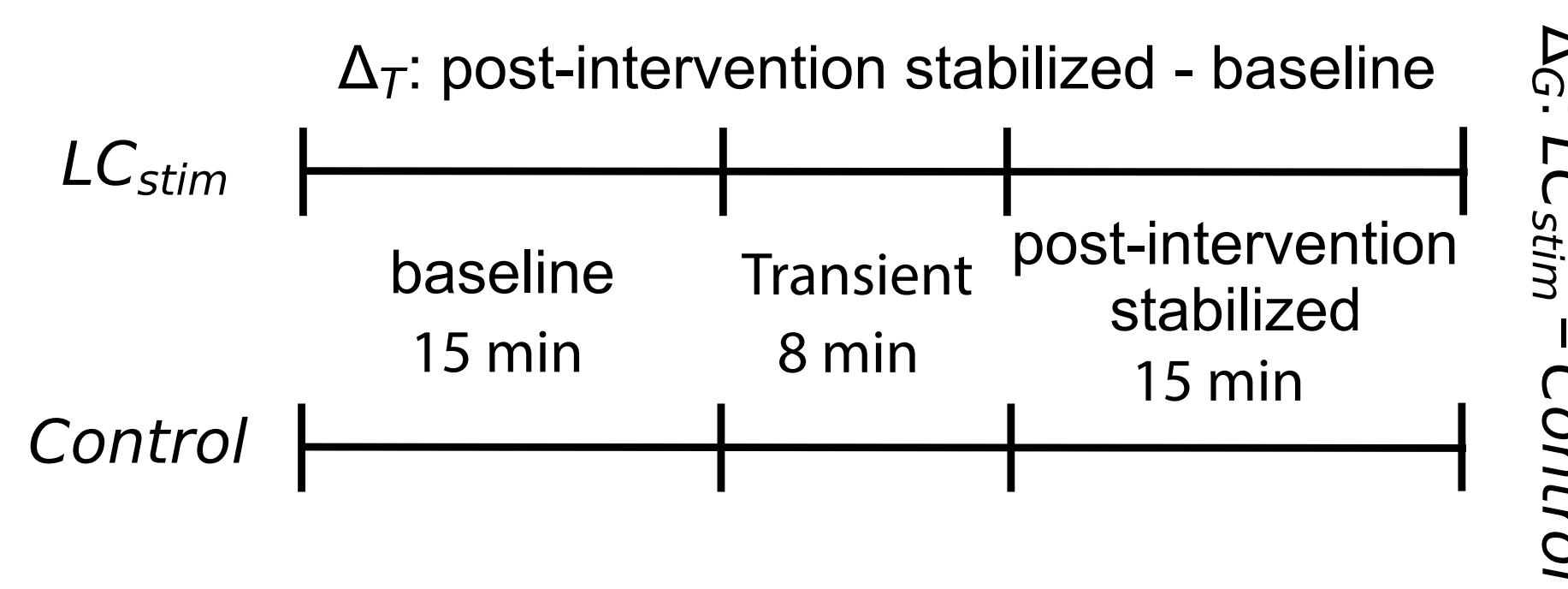
Chemogenetic activation of locus coeruleus (LC) in mouse to study brainwide neuromodulation by norepinephrine



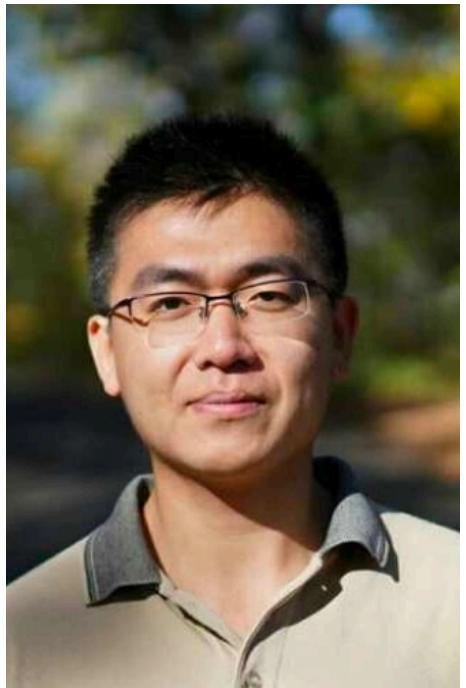
Collaboration with Valerio Zerbi (ETH)

Zerbi et al. (2019) *Neuron*

LC stimulation effects on BOLD dynamics



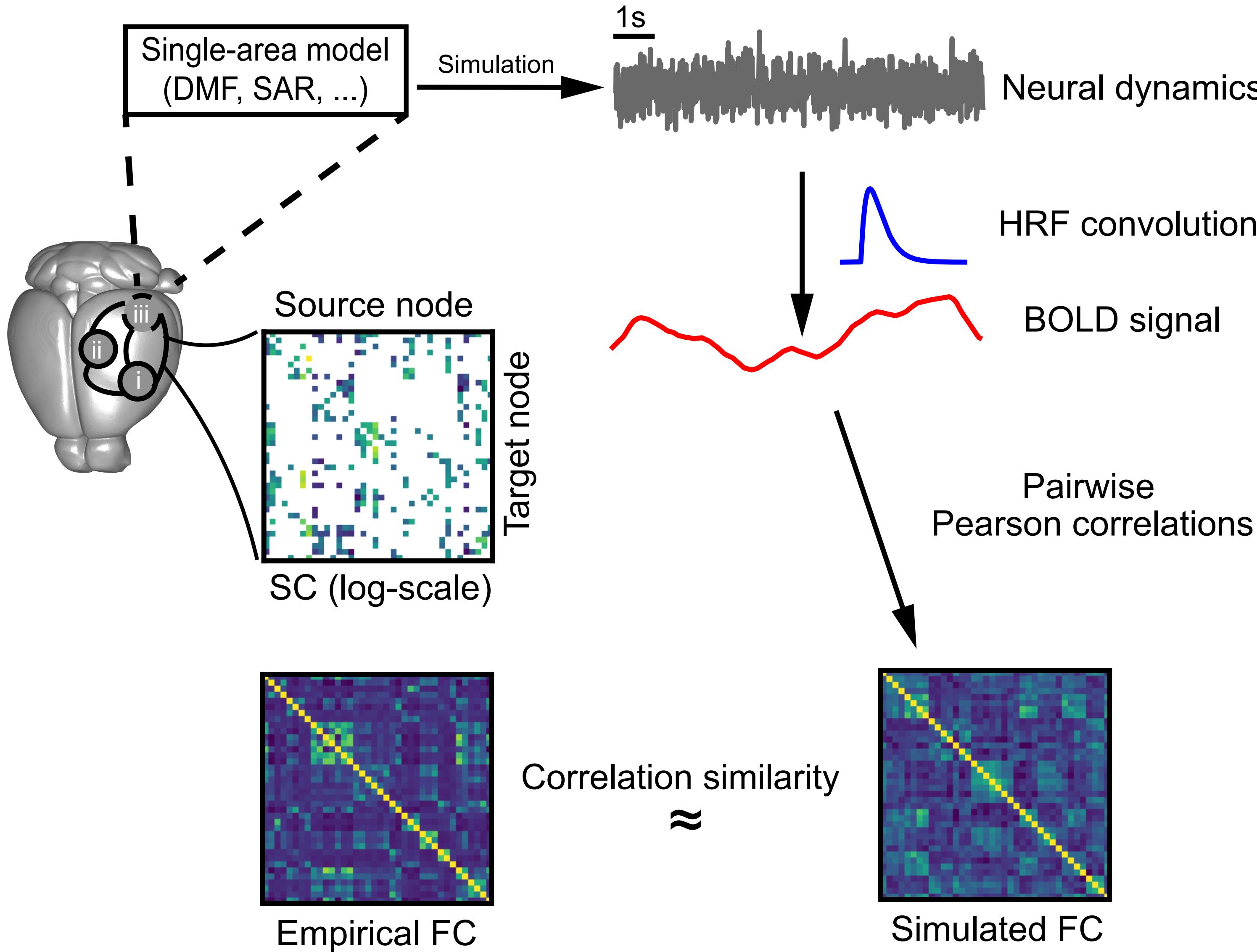
Large-scale model of mouse cortical BOLD dynamics



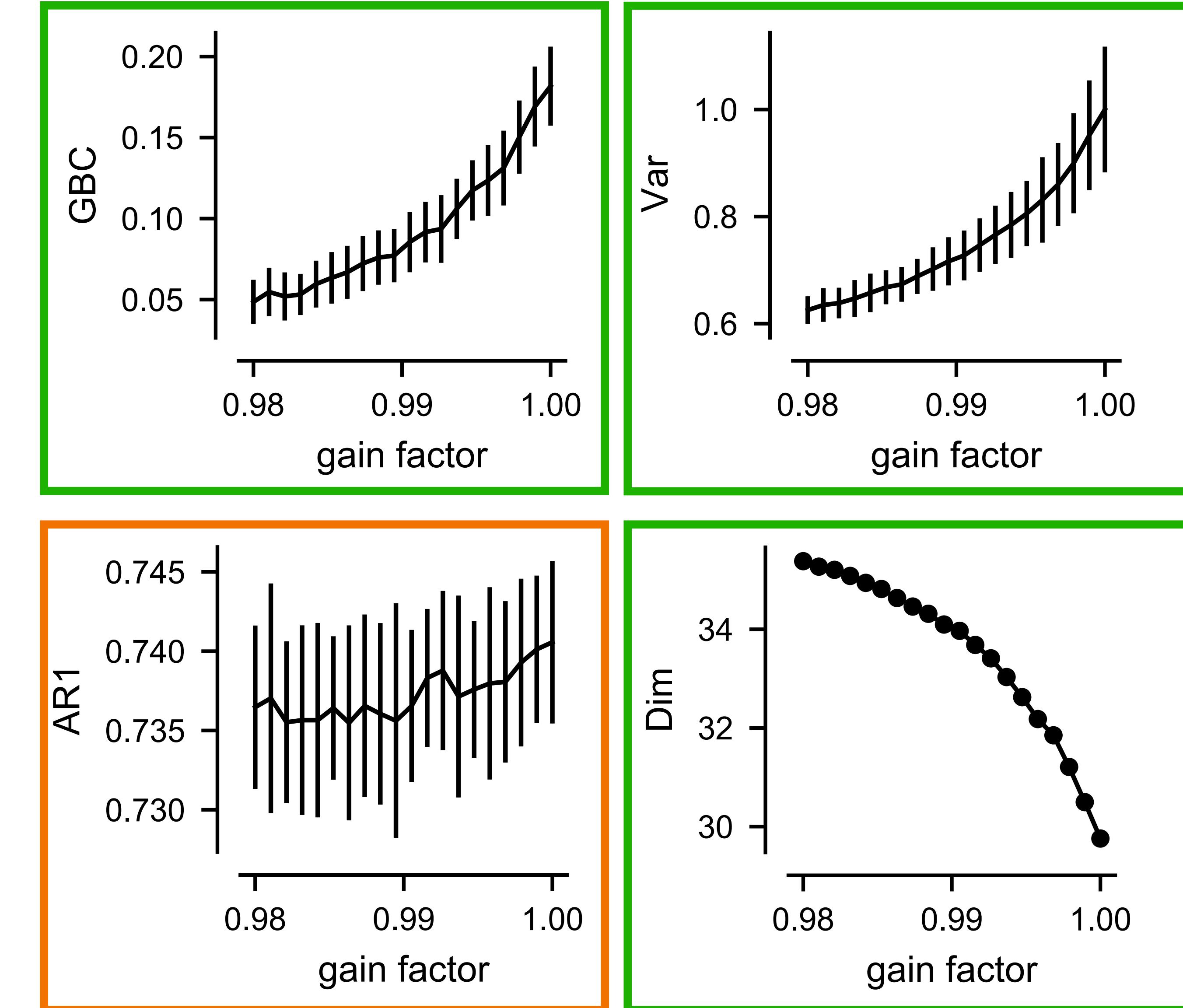
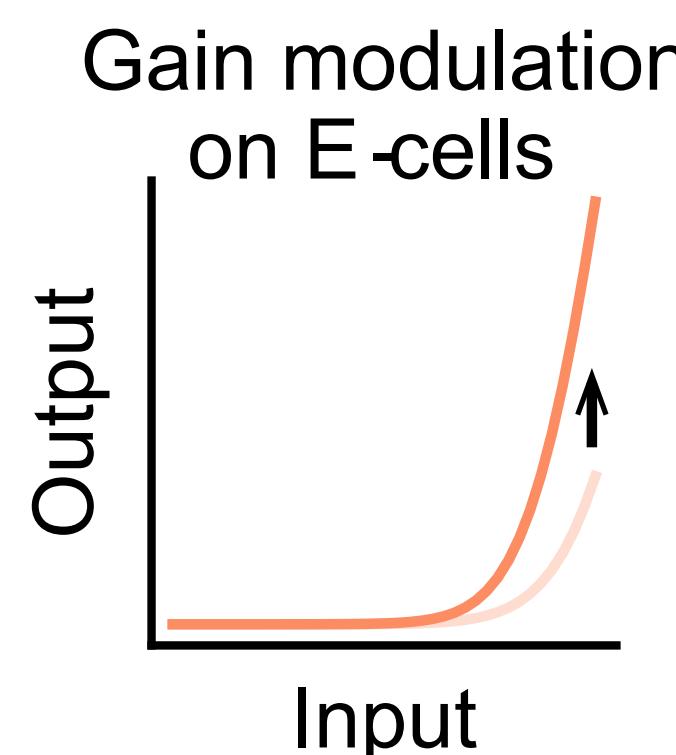
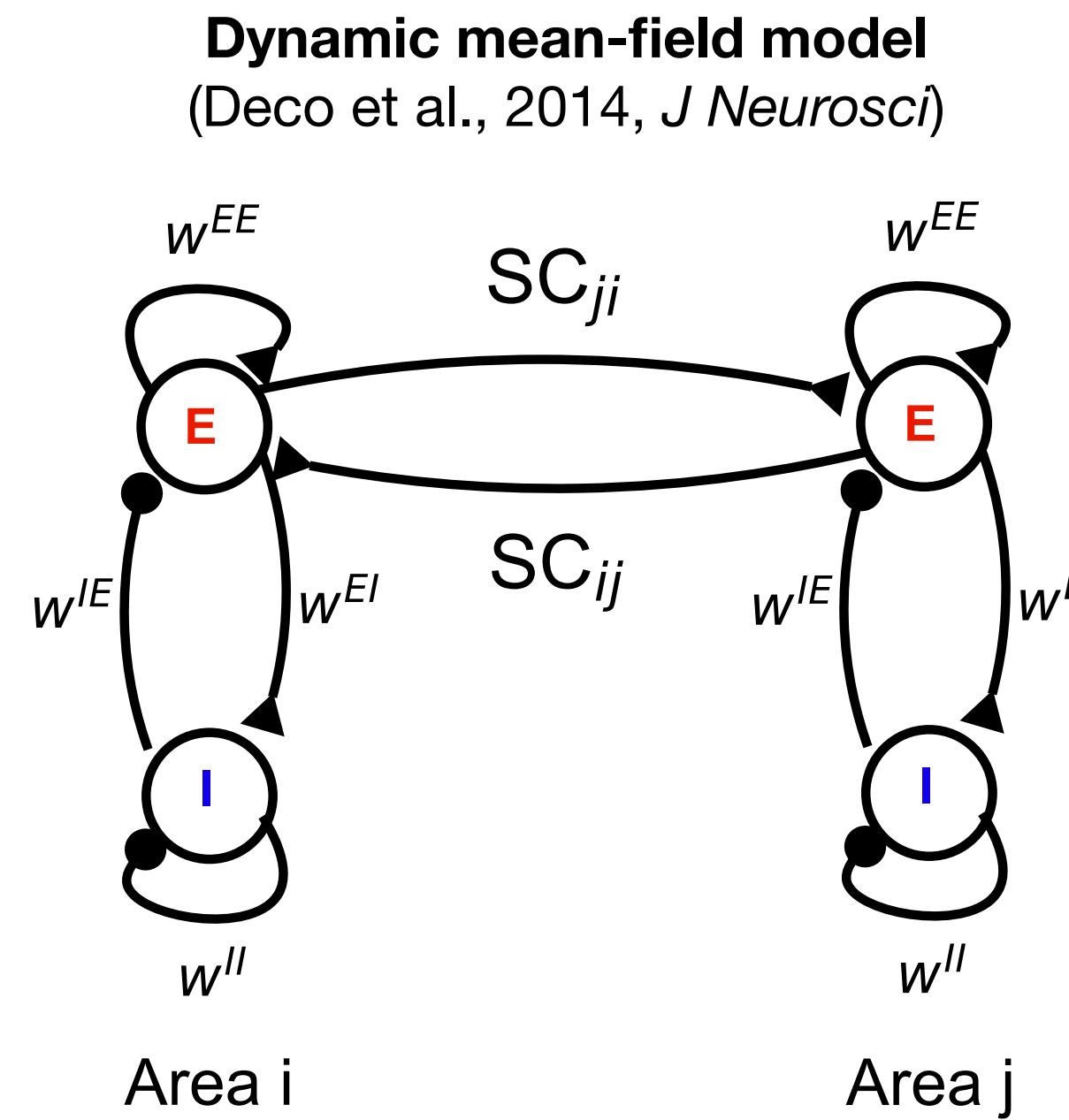
Daming Li



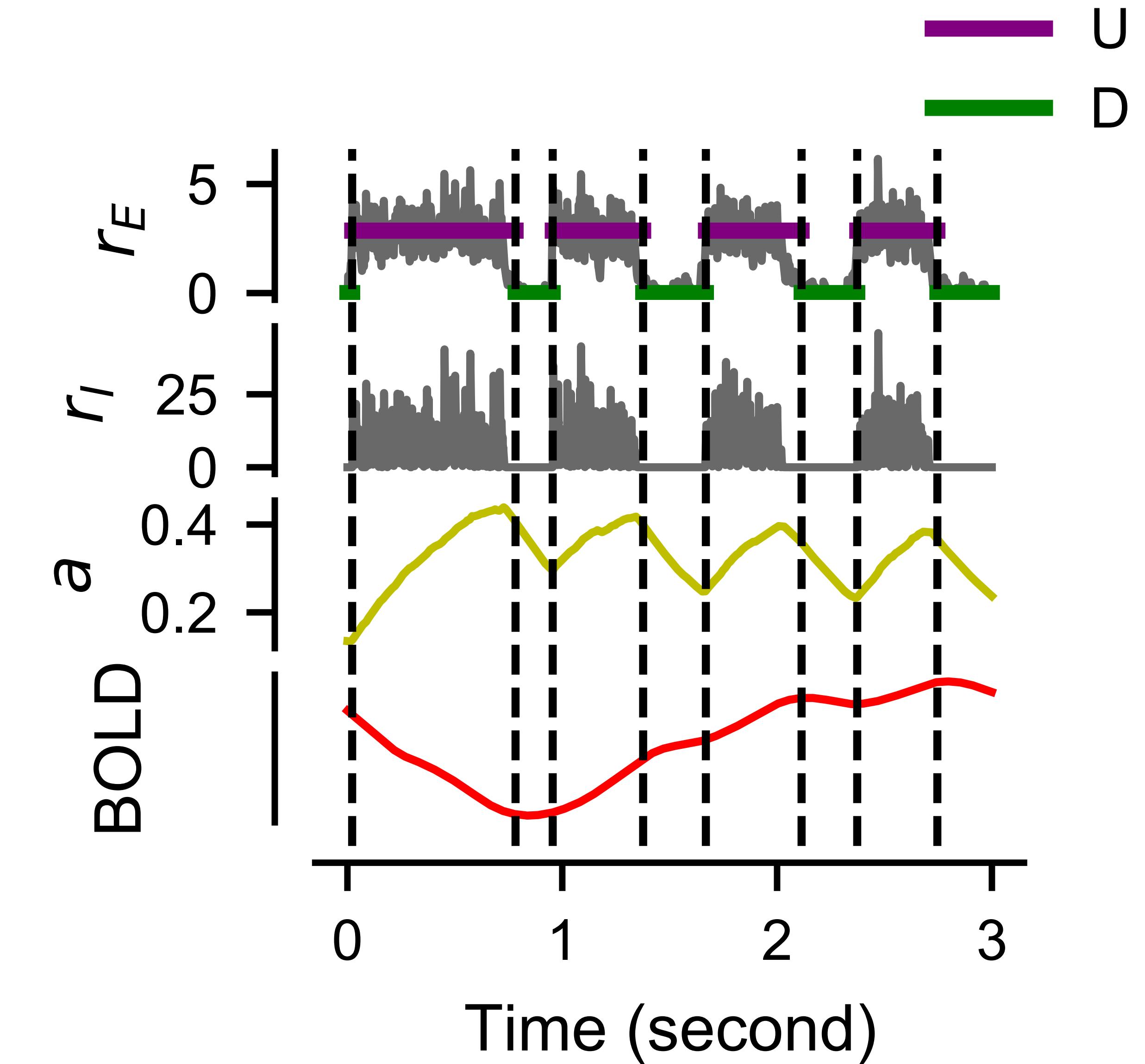
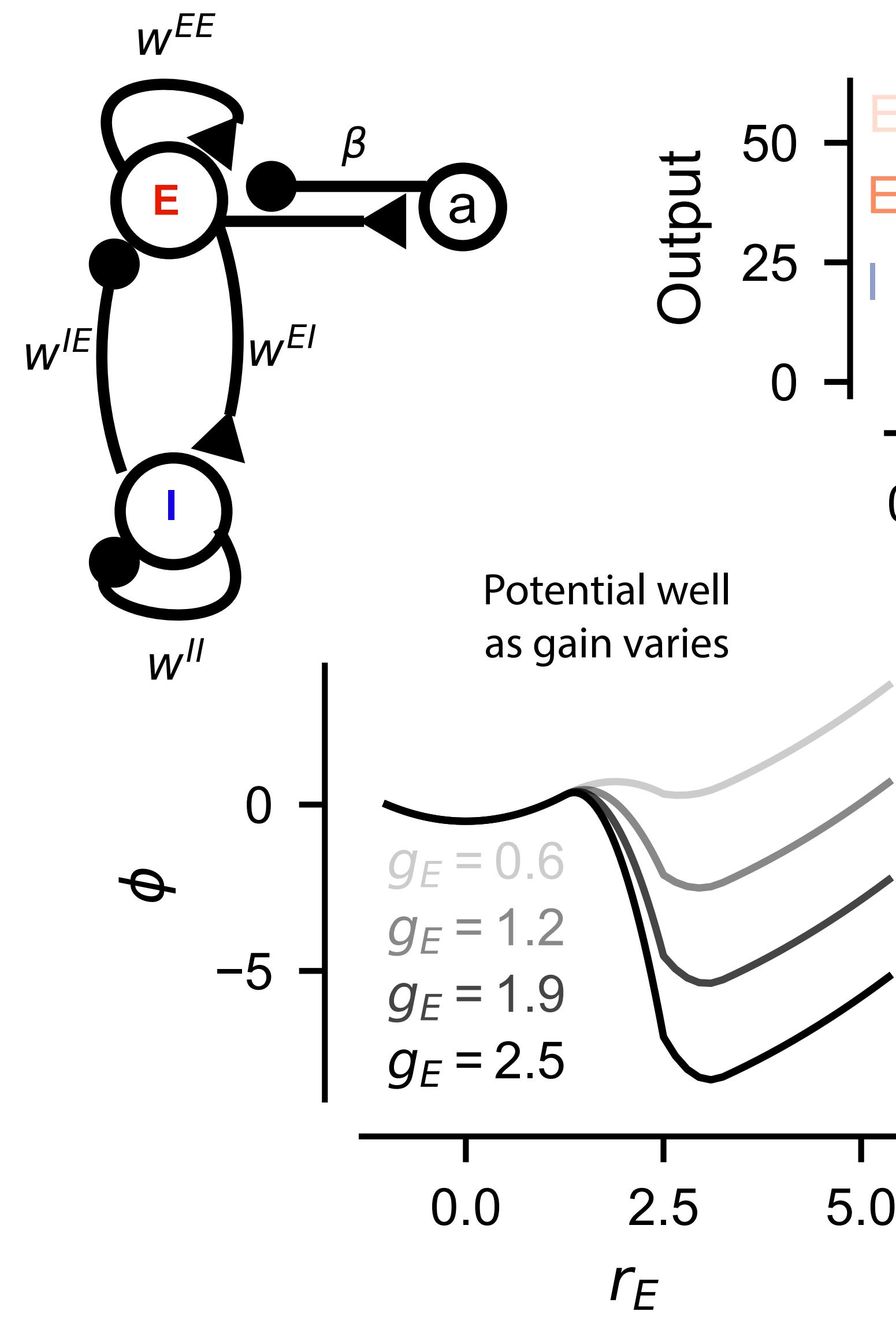
Qinglong Gu



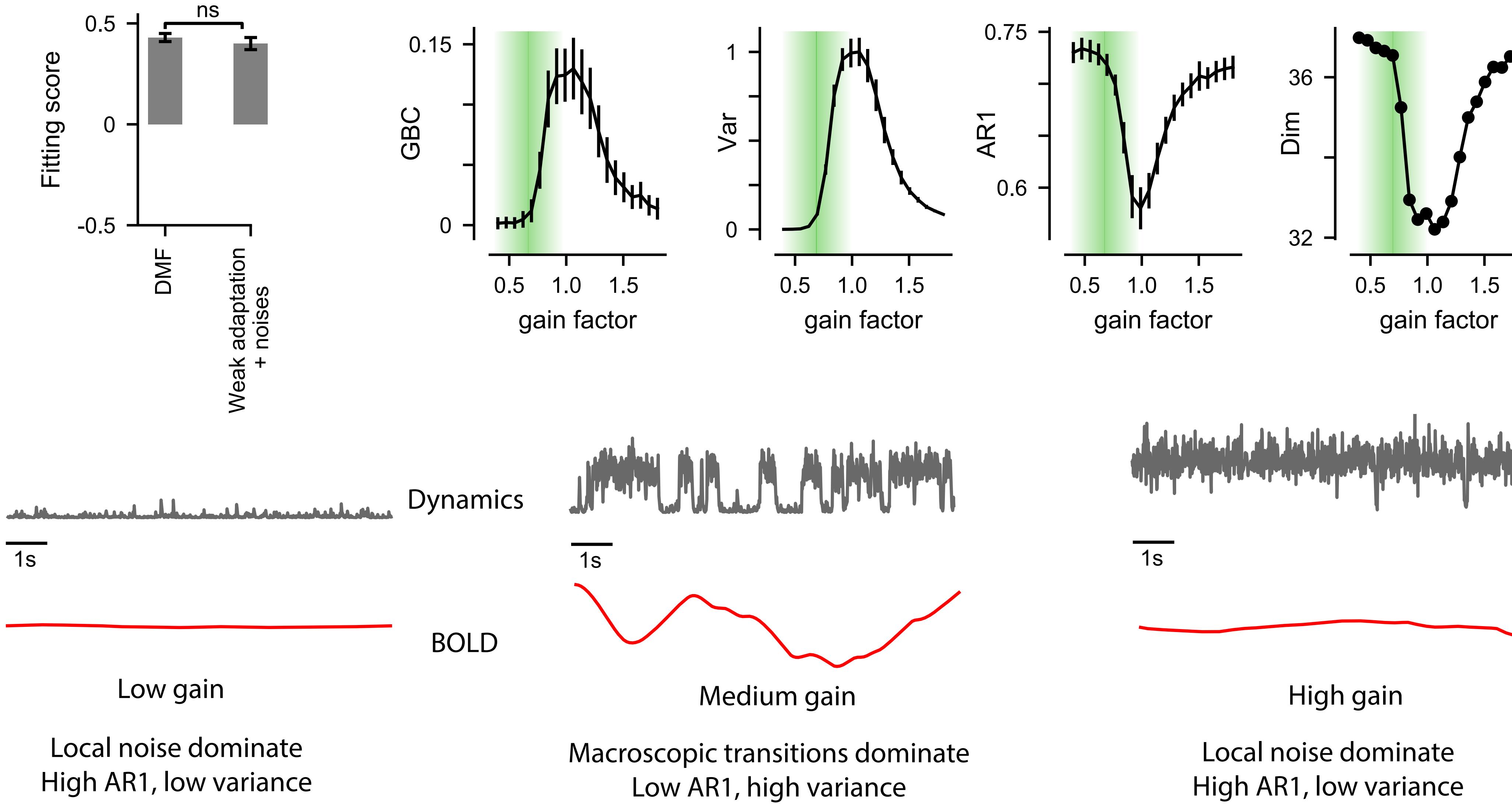
Dynamic mean-field model of mouse cortex with gain modulation



Local E-I circuit with adaptation with bistable dynamics

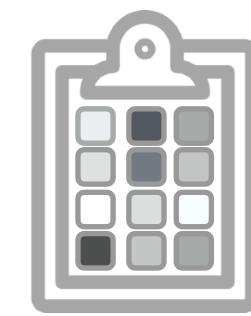


Gain modulation in bistable model captures LC stimulation effects

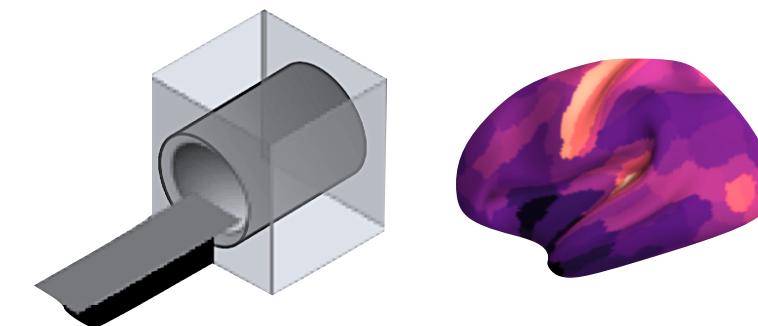


Conclusions

PERSONALIZED
BEHAVIORAL
PROFILES



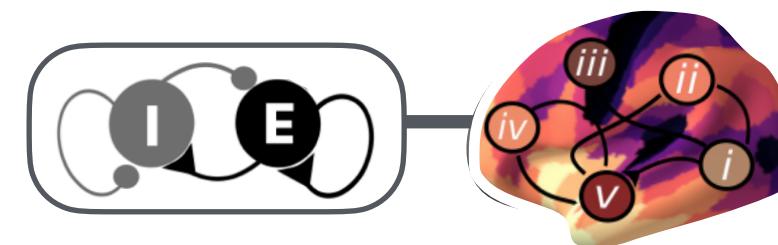
NEURAL
BIOMARKERS



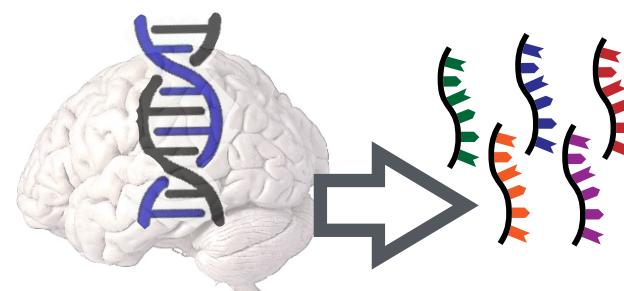
PHARMACOLOGICAL
NEUROIMAGING



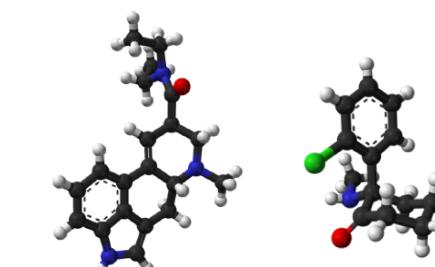
BIOPHYSICAL
CIRCUIT
MODELING



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

Acknowledgements



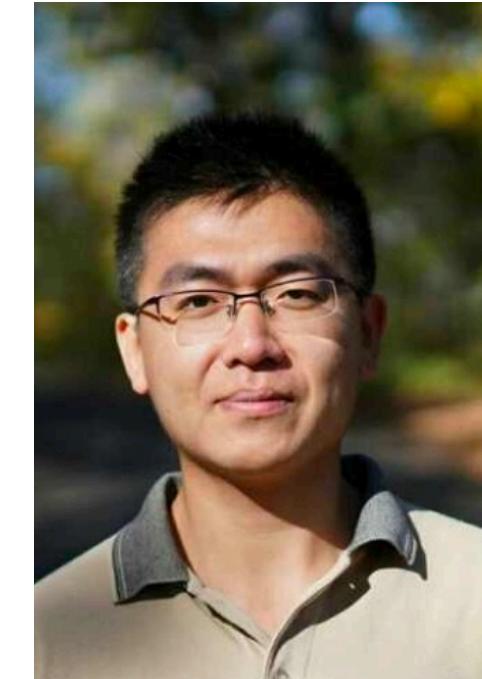
Murat Demirtaş



Joshua Burt



Rachel Cooper



Daming Li



Qinglong Gu

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Alan Anticevic
John Krystal
Katrín Preller

Stam Sotiropoulos
Franz Vollenweider
Valerio Zerbi



R01 MH112746

