

## OVERVIEW

**Problem:** Diffusion MRI (dMRI) tractography is used to estimate structural connectivity (SC) lacks directional information about white matter pathways.

**Approach:** Using the **Higher Order Network Diffusion (HONeD) Model** [1], we learn a diagonal matrix (**A**) parameterized by gene gradients to make SC (**C**) directional. SC directionality is learned by minimizing the Lyapunov residual for a stationary covariance.[2]

**Impact:** This framework offers a promising method to infer the directions of white matter pathways. Applications span cognitive neuroscience, developmental neuroscience, and neurodegenerative diseases.

## DATASETS & METHODS

### Human:

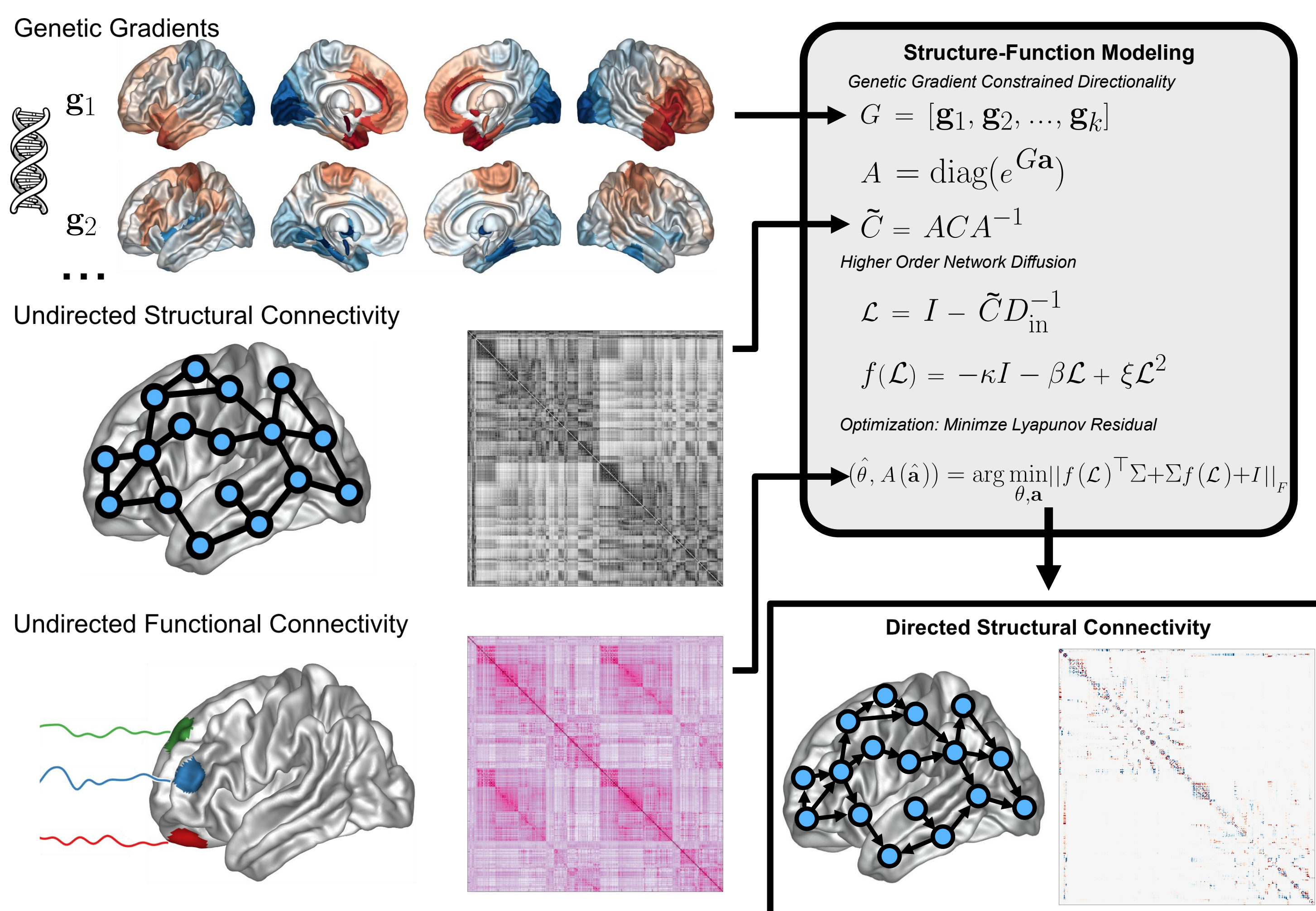
770 Healthy young adult subjects from the Human Connectome Project S1200 release [3] with resting state fMRI. SC and fMRI data processed into the Schaefer 400 + 14 subcortical atlas with micapipe.[4]

**C. elegans:** Ca<sup>2+</sup> imaging signal propagation maps and synapse count neuronal connectivity from 273 neurons across 113 individual worms. [5]

**Mouse:** 9 mouse fMRI parceled in the Allen Brain Atlas (ABA) with 426 regions, and tracer-based directionality using the ABA connectome. [6,7]

**Macaque:** 9 Non-human primates' fMRI with a macaque consensus SC and tracer data from CoCoMac parceled in the RM atlas with 86 regions. [8]

**All datasets had species-specific neuron/region level transcriptomics provided by public datasets.** [9-11]

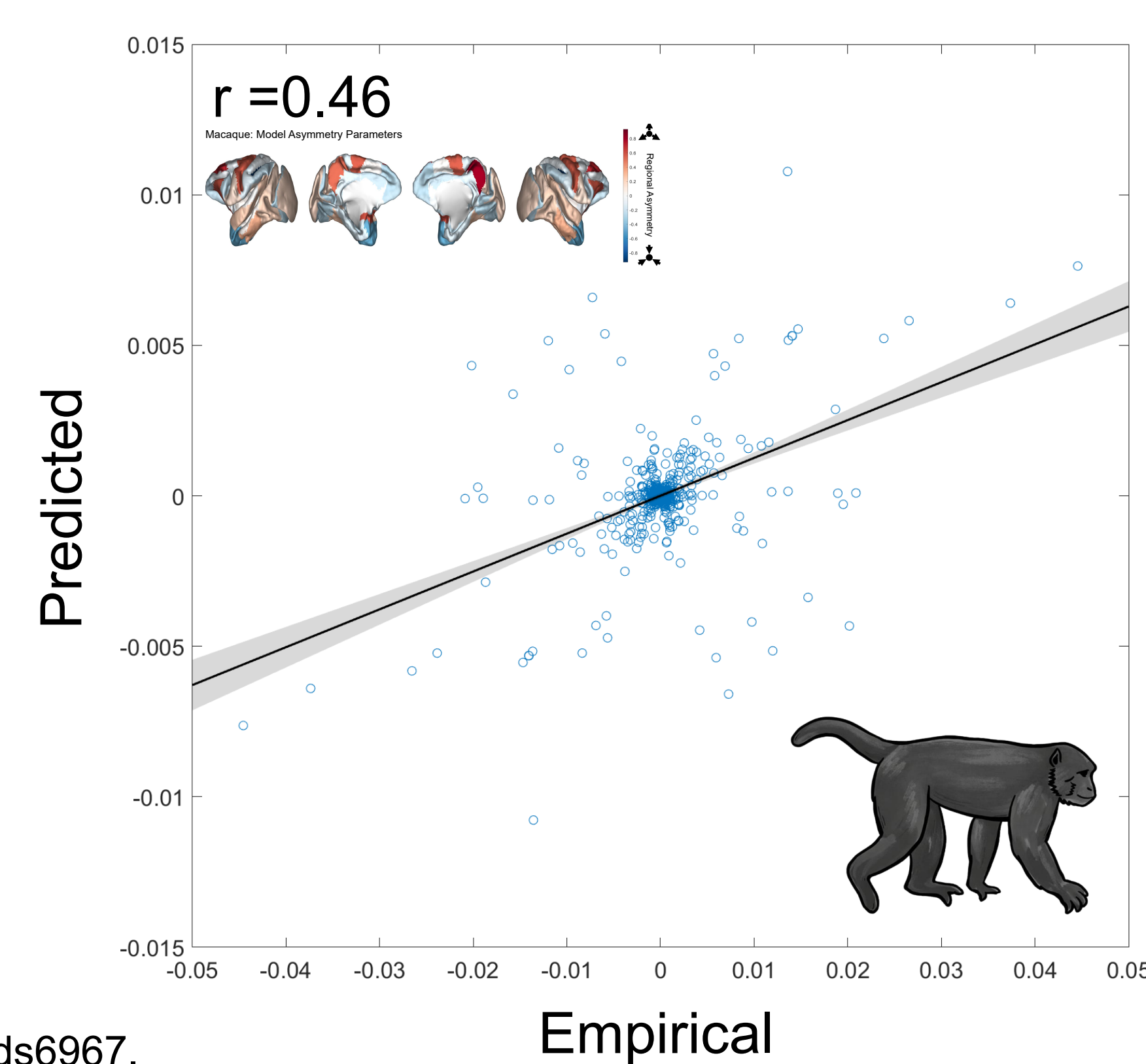
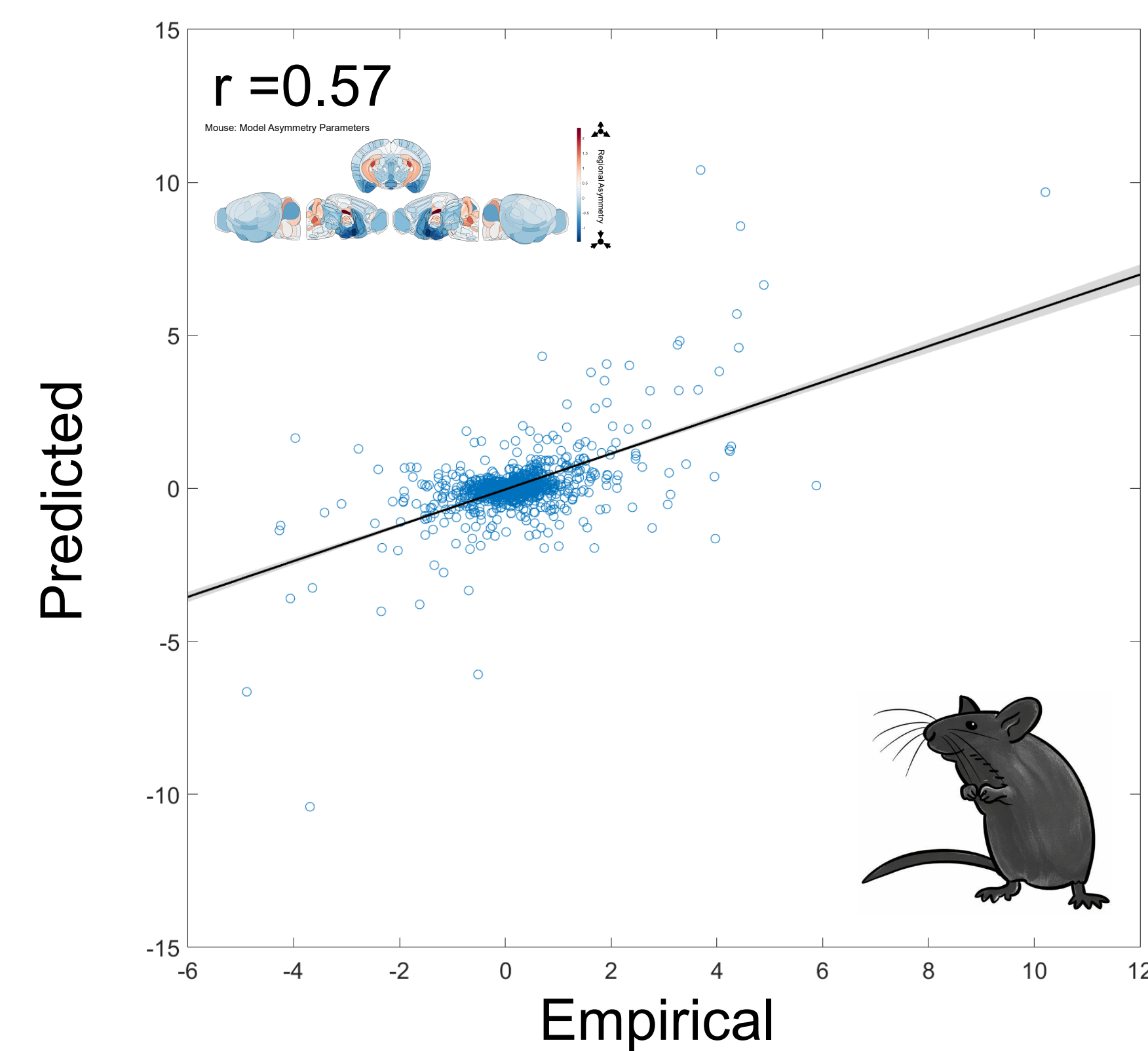
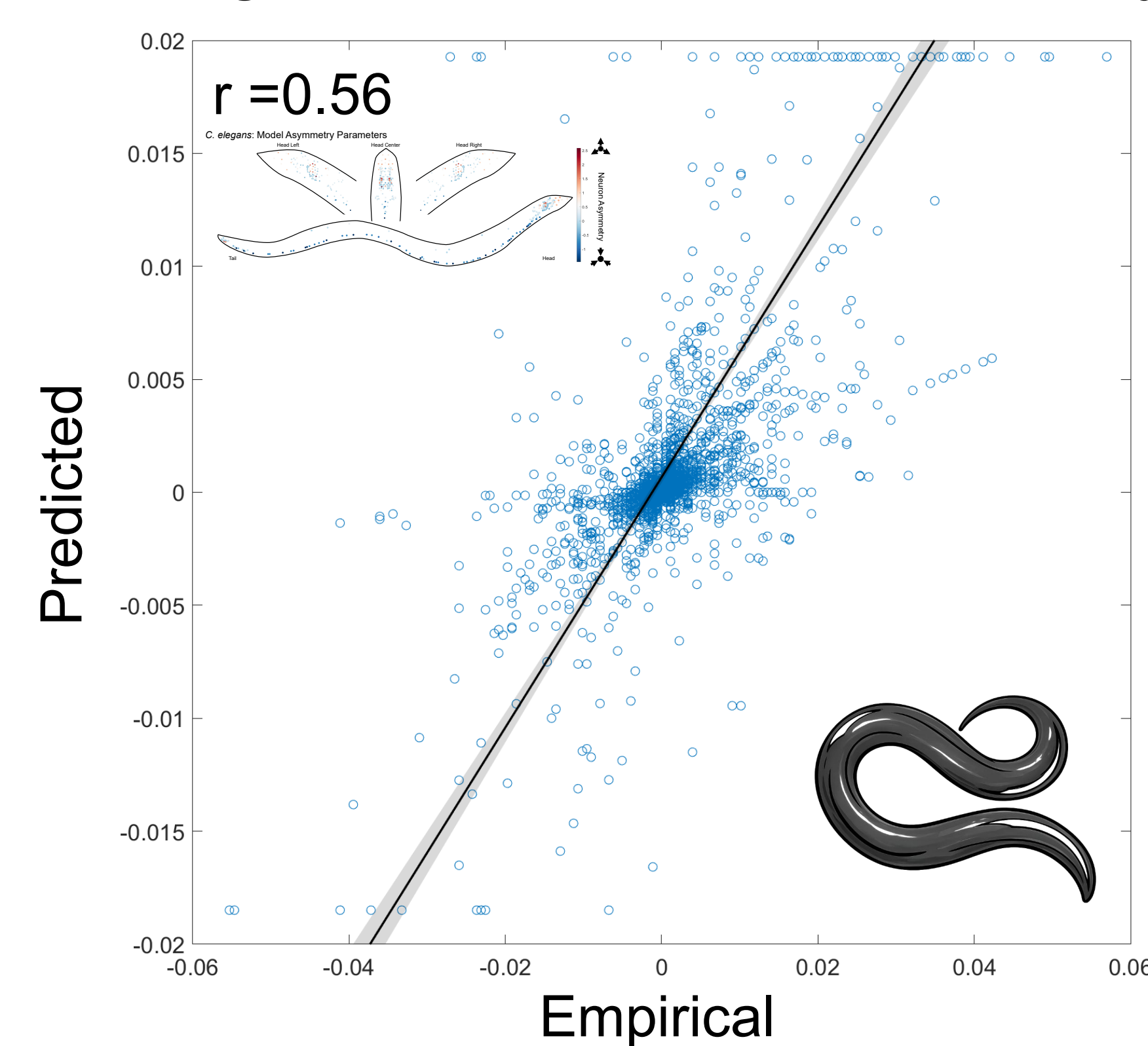


## RESULTS

### Cross-Species Validation

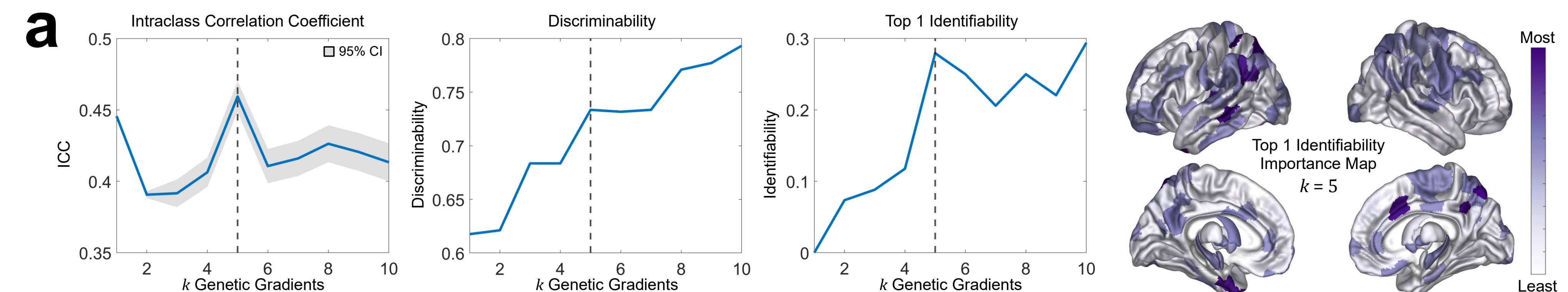
- Model-predicted directionality significantly correlated with ground-truth directed edges in all three species.
- The optimal numbers of genetic gradients was also different in each species (*C. elegans*: k=3; Mouse: k=5; Macaque: k=1).

### Edge-Wise Skew Directionality

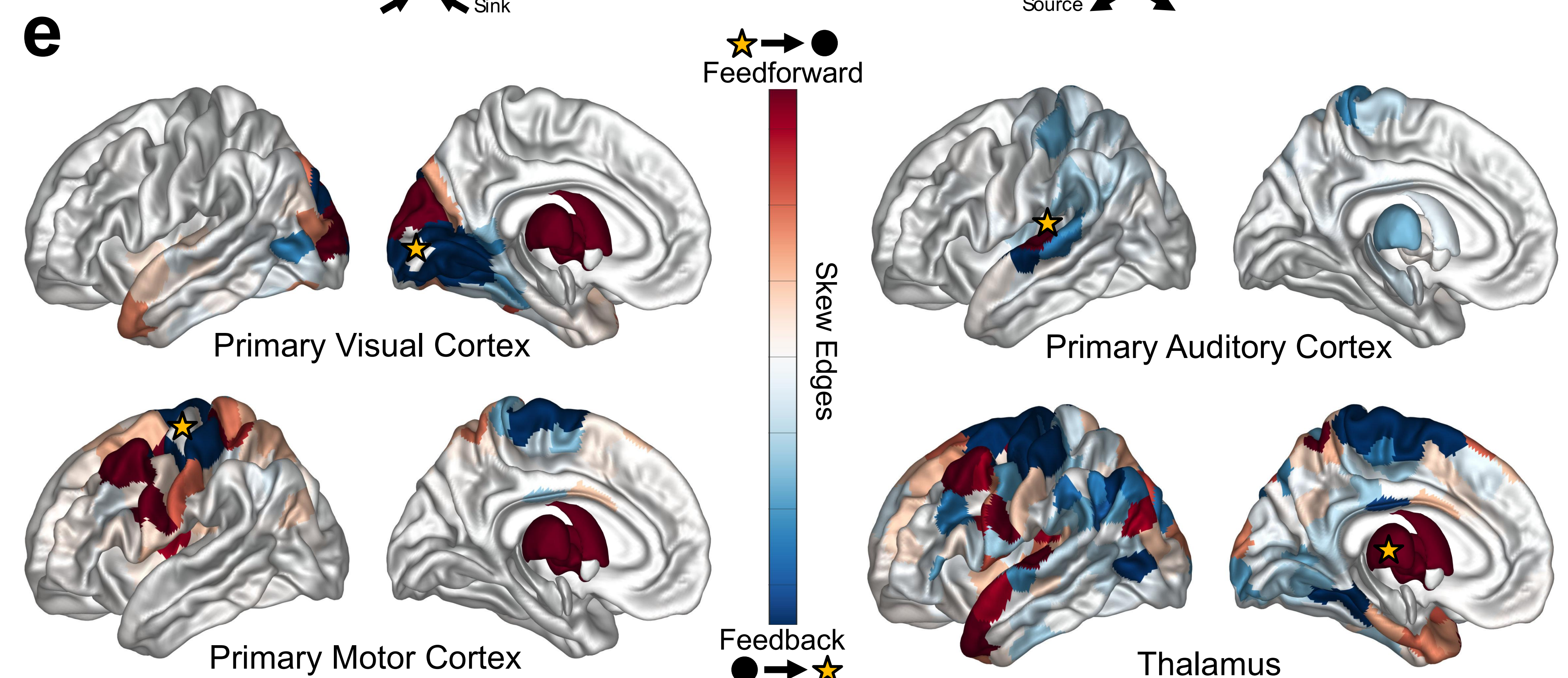
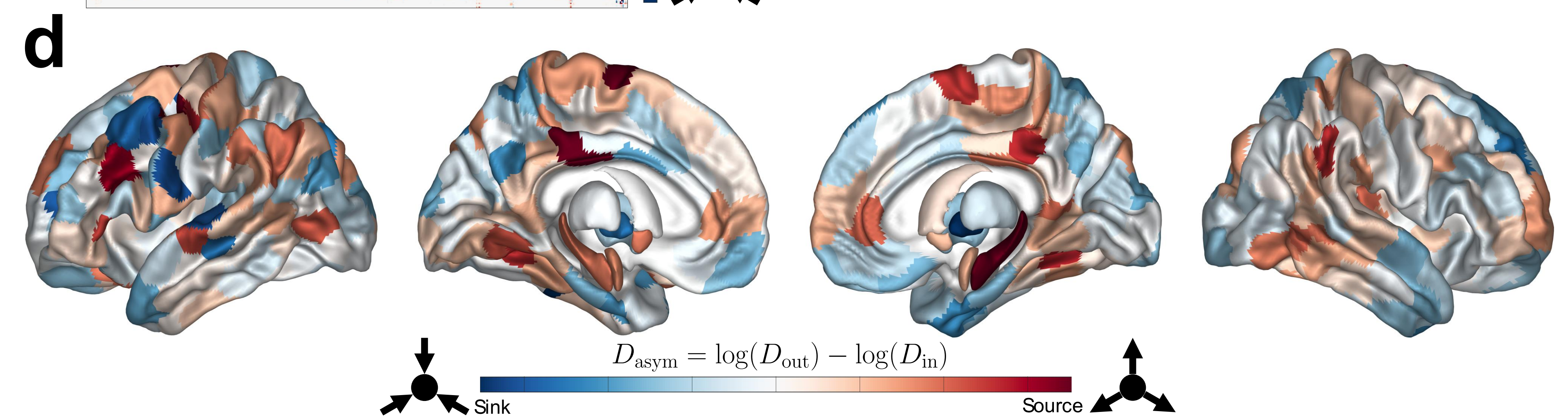
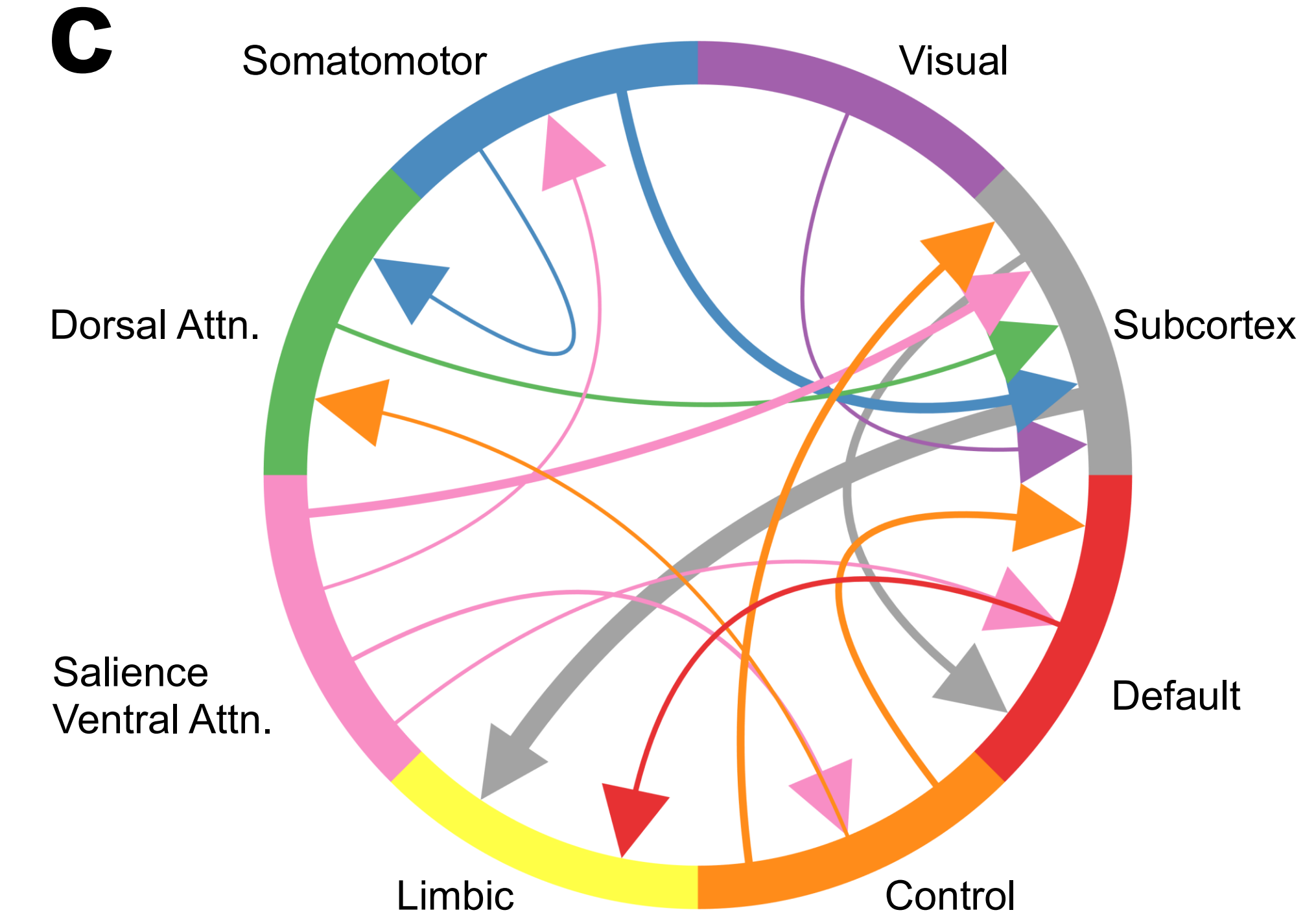
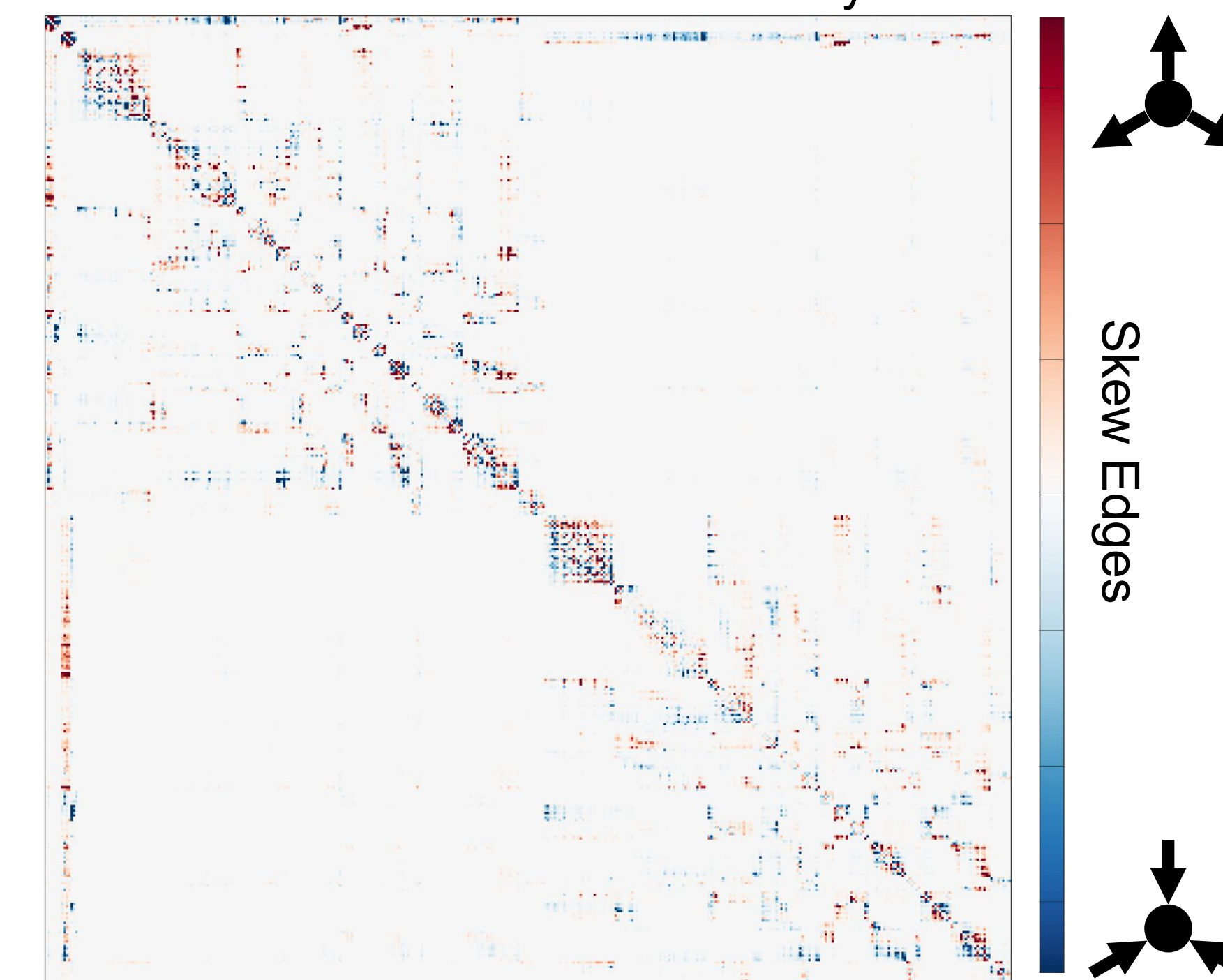


### Human Estimated Directionality

- Five genetic gradients were the fewest that provided the best overall test-retest reliability.
- Directionality estimates were strongest *within* hemispheres, with homologous regions sharing similar degree asymmetry. The right hemisphere had less pronounced directionality.
- Most resting state networks (RSNs) show strong directionality toward the subcortex.
- Regional Sources:** Hippocampus, temporal-parietal junction, anterior/posterior cingulate.
- Regional Sinks:** temporal poles, ventromedial prefrontal cortex.
- We found evidence for strong feedback connections in primary sensory pathways.



### Consensus Skew Connectivity



## ACKNOWLEDGEMENTS

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