Causal Discovery for fMRI data: Challenges, Solutions, and a Case Study

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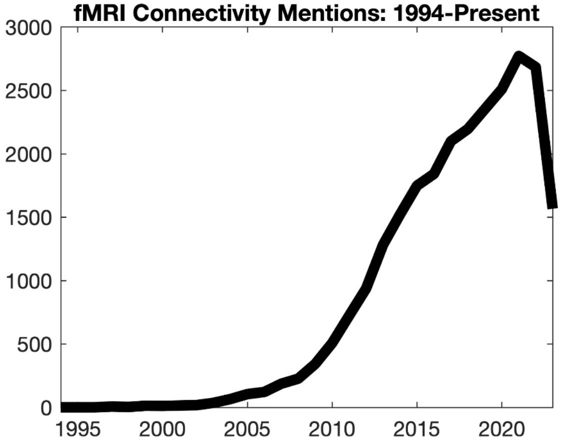
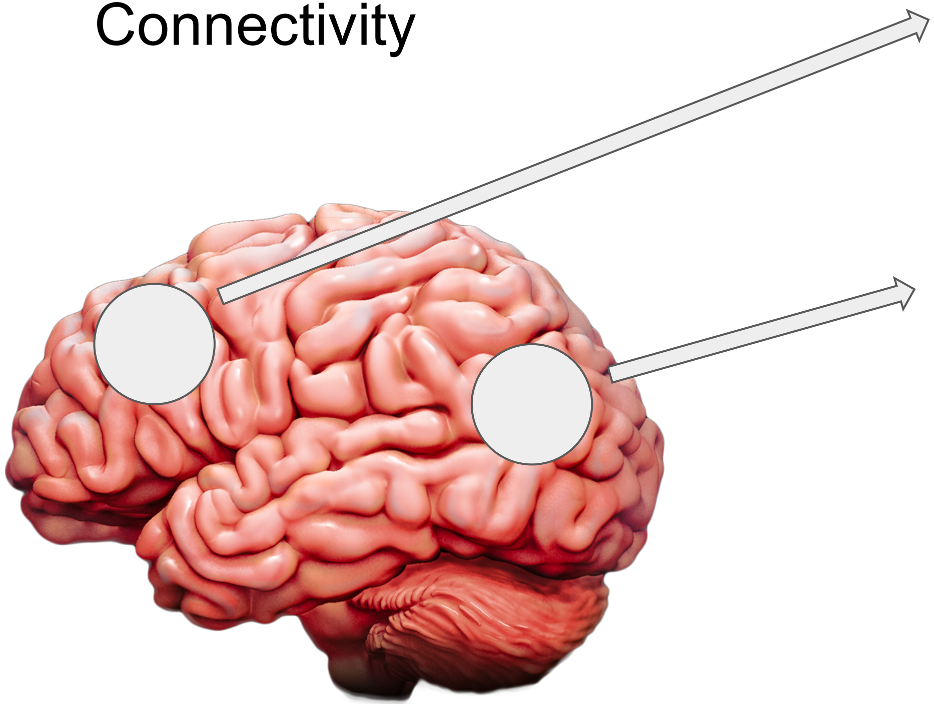
fMRI Connectivity Beginning and Now

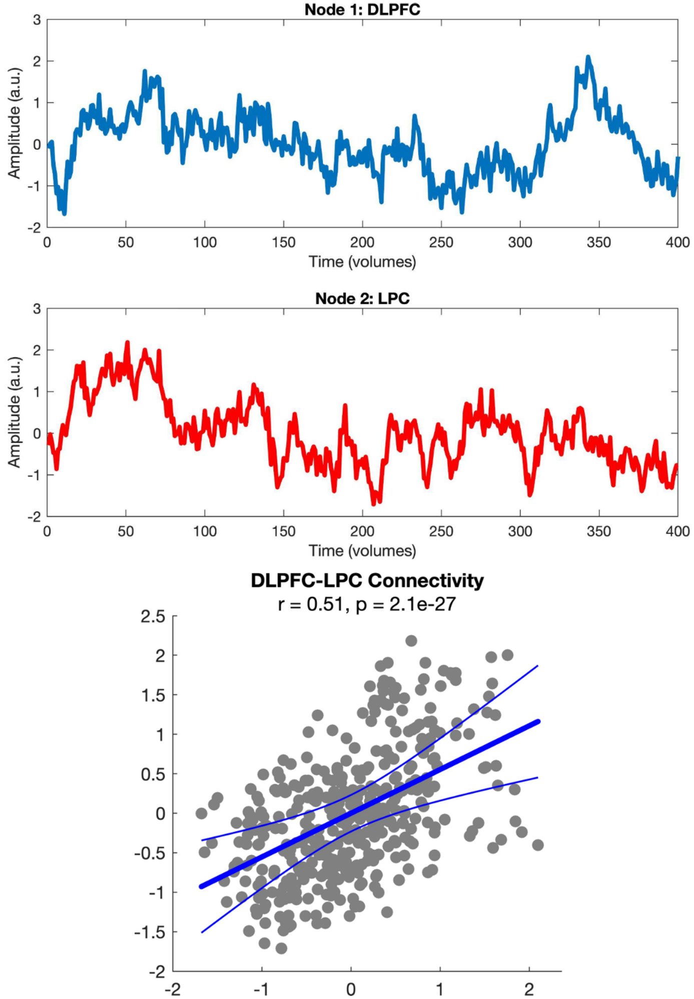
- 1995: Bharat Biswal discovers correlations in the time courses of motor regions during movement using fMRI (cited >10,000 times)
  - “It is concluded that correlation of low frequency fluctuations, which may arise from fluctuations in blood oxygenation or flow, is a manifestation of functional connectivity of the brain.”

- Today: fMRI connectivity studies dominate the scientific conversation
  - YA-HCP: >1000 subjects, cited >4000 times
  - UK BioBank: >10,000 subjects, goal of 100,000, cited >1000 times
  - ABCD: >10,000 subjects, cited >500 times

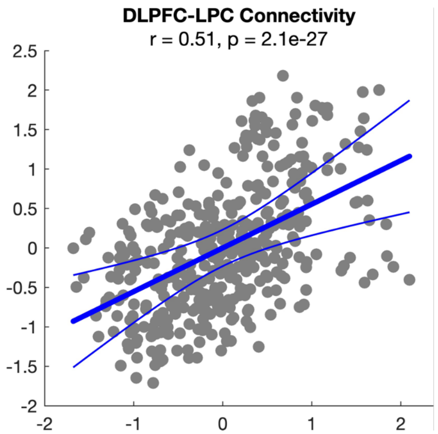


Correlation-based fMRI Connectivity



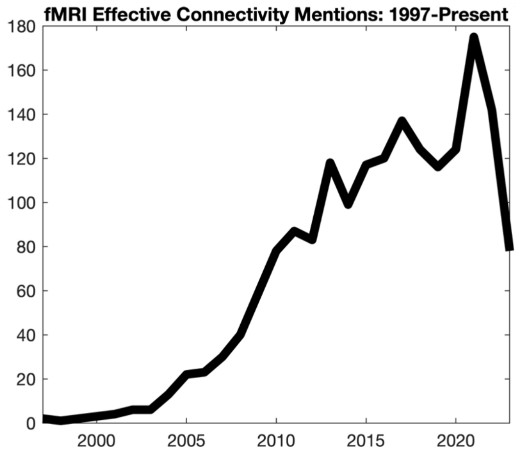


Correlation-Based fMRI Connectivity - Limitation



fMRI Effective Connectivity

- 1995: Karl Friston applies a nonlinear regression model to show modulatory directional influences between V1 & V2
  - This method is later generalized into PPI (Psychophysiological Interaction) analysis, and into DCM (dynamic causal modeling)
- 1997-2000: Ed Bullmore, Karl Friston, and others begin applying SEM (structural equation modeling) to test hypotheses of directed connectivity
- 2002: Culmination: Brain Connectivity Workshop (Rolf Kotter, Karl Friston)
  - First conference presentations of Dynamic Causal Modeling and Vector Autoregression for imaging data
- 2003: First appearance in the literature of DCM (Friston) and MVAR (Goebel)
- Today, these two techniques still dominate the effective connectivity literature



Interim: Methods for Building Directed fMRI Networks

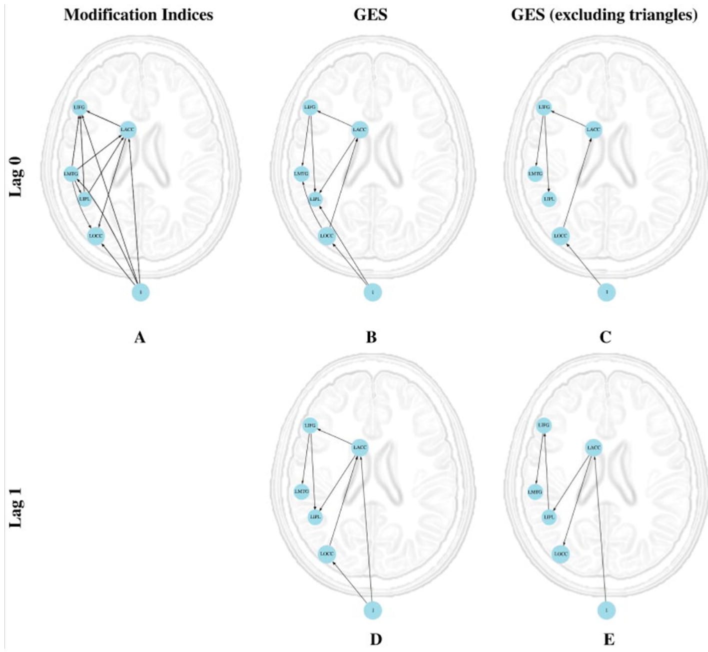
- Lag-based (Granger Prediction, Transfer Entropy)
  - Pros:
    - Easy to compute
    - Well-cited in neuroscience
  - Cons:
    - Differential lags in fMRI BOLD data due to tissue susceptibility, vasculature

fMRI has time lag issues that make this not work

- Model-Based (Dynamic Causal Modeling)
  - Pros:
    - Hypothesis testing
    - Confirms/denies a mechanistic model
  - Cons:
    - Small search space
    - Requires a priori model specification

This works well for fMRI but does not scale up well enough for whole-brain

Causal Discovery - an alternative approach to fMRI connectivity



- Ramsey et al. (2010; NeuroImage) expanded on limitations of previous causal connectivity methods, and proposed to address them using graphical causal models, notably, GES and IMaGES

1. What decision points will be faced by researchers applying CDA to fMRI data?

2. How can we begin to address the researcher degrees-of-freedom problem in this arena?

Practical Challenges of Applying CDA to fMRI Data: an Outline for the Remainder of the Talk

C1: Preprocessing
C2: Cycles
C3: Undersampling
C4: Latents
C5: Spatial Smoothing
C6: High Dimensionality
C7: High Density
C8: Scale-Free Structure
C9: Limited samples

GANGO Method: a Case Study

- Recently, we developed the GANGO method for fMRI causal connectivity (Rawls et al., 2022; NeuroImage). We had to make these decisions!
- In the following, we describe data characteristics that we used to make these decisions

ELSEVIER

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

The resting-state causal human connectome is characterized by hub connectivity of executive and attentional networks

Check for updates

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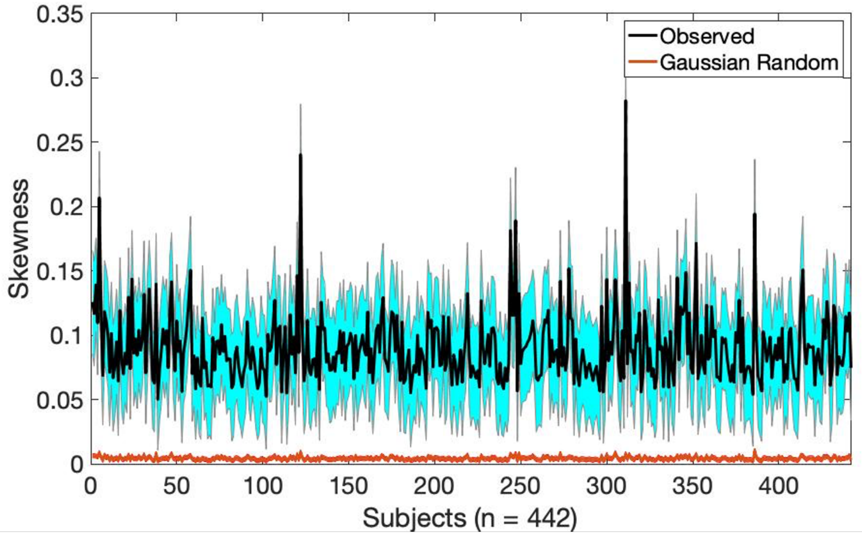
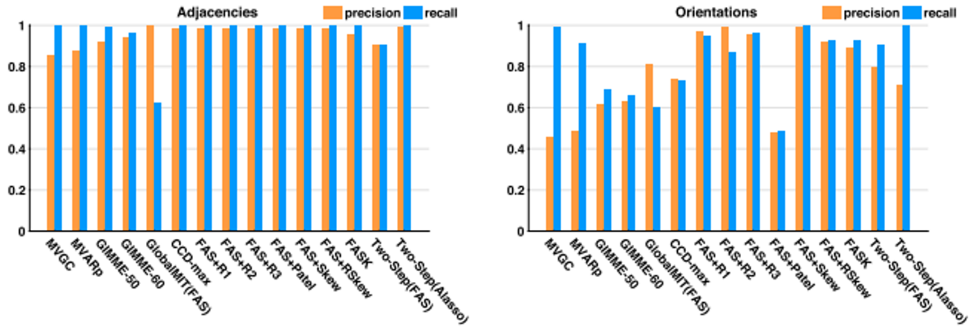
Challenge 1: Preprocessing

- Minimal HCP preprocessing (Glasser et al., 2013) was used to preserve as much non-Gaussian signal as possible



Challenge 2: Cycles

- We determined orientations using the RSkew method, which can solve for >=3-cycles



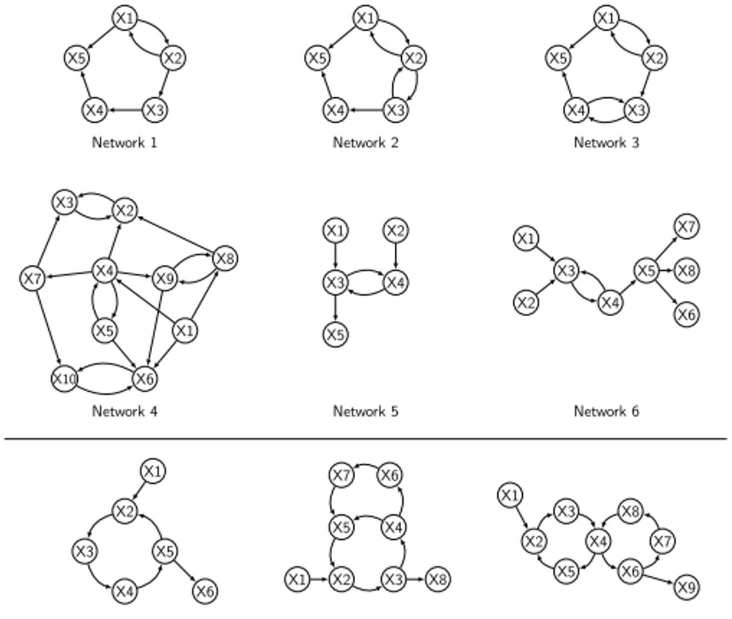
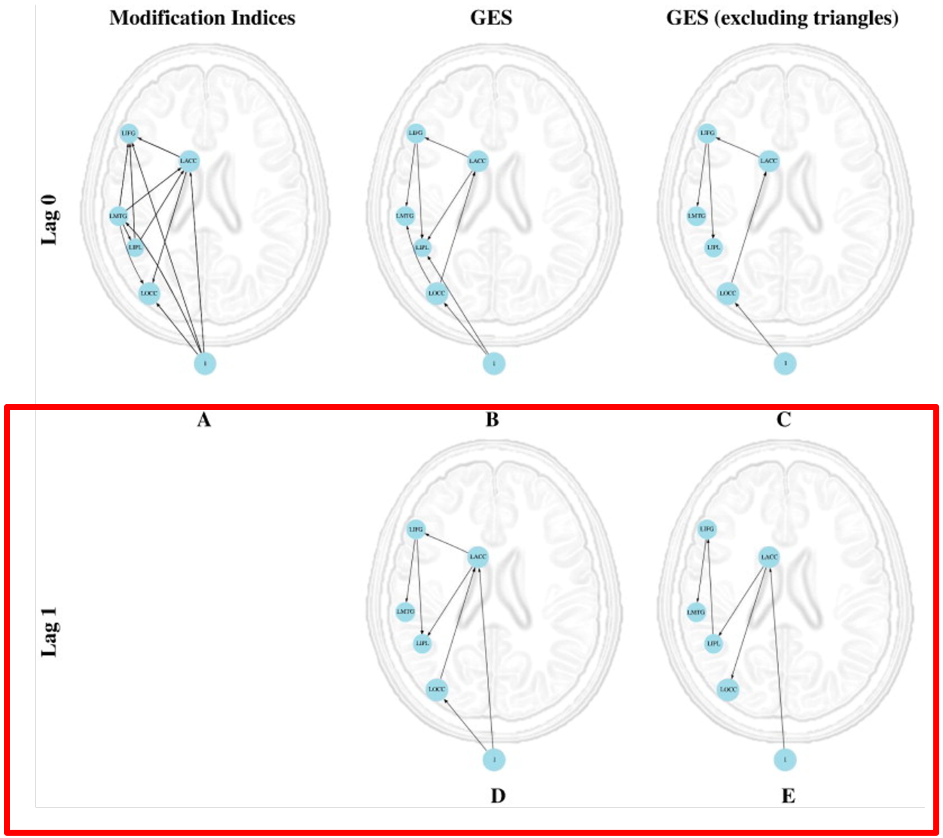


Figure 1. Networks containing 2-cycles: *Networks 1* to *6*; and higher degree cycles: *Networks 7* to *9*.

Sanchez-Romero et al., 2019

Challenge 3: Undersampling

- Time series element of data was ignored, and parcellated time series were analyzed as cross-sectional data
- This approach does not use the available time-series information, but it avoids relying on the heavily undersampled time dimension
- Future applications could also consider conditioning on prior time steps to explicitly model this problem (as in Ramsey et al., 2010)



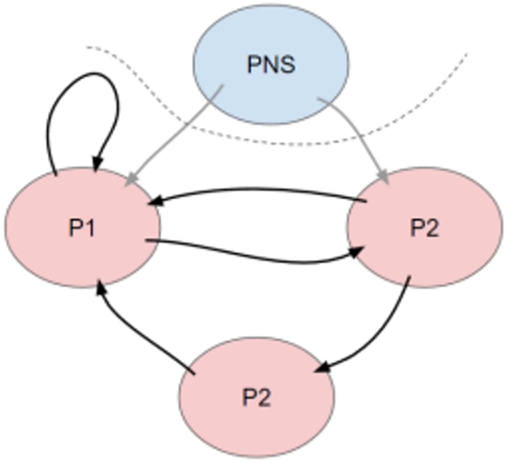
Ramsey et al., 2010

Challenge 4: Latents

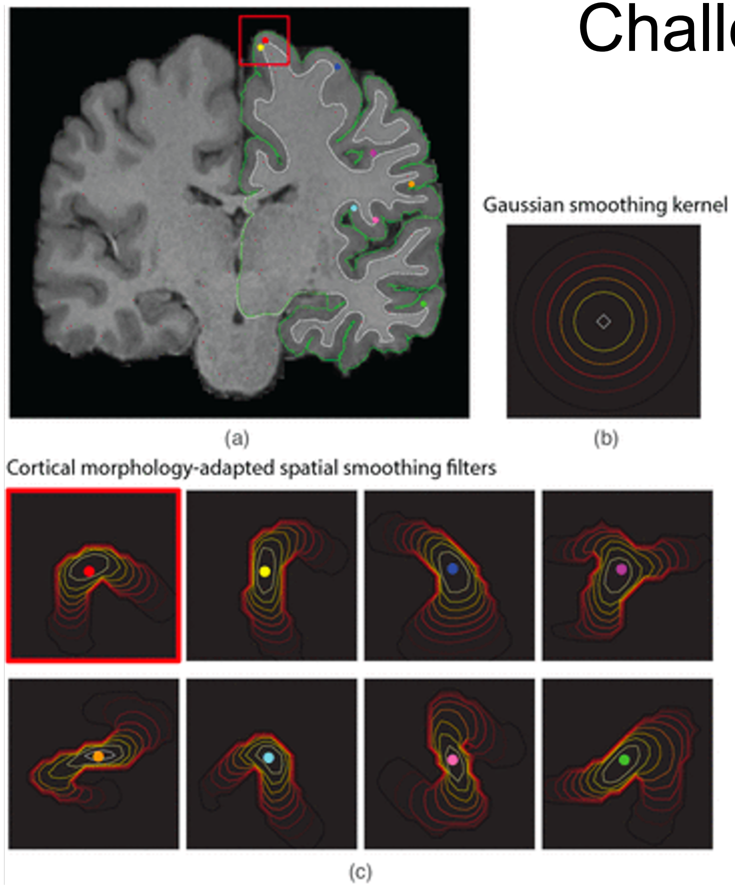
- No explicit attempt was made to deal with latent confounding

- Findings were reported at an aggregate level rather than reporting individual edges

- Progress is needed in the area of causal discovery of latent variables



Challenge 5: Spatial Smoothing



Behjat et al., 2021

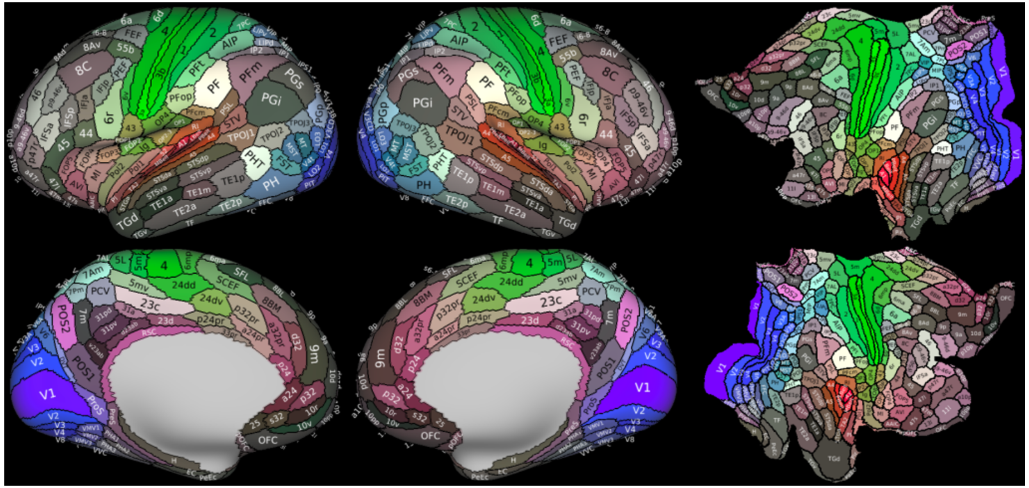
- The data were minimally smoothed in surface space, avoiding smoothing over gyri/sulci

- Data were analyzed at the level of parcels, reducing impacts of smoothing

Challenge 6: High Dimensionality

- Data were high-dimension, since we used a 360-node cortical parcellation

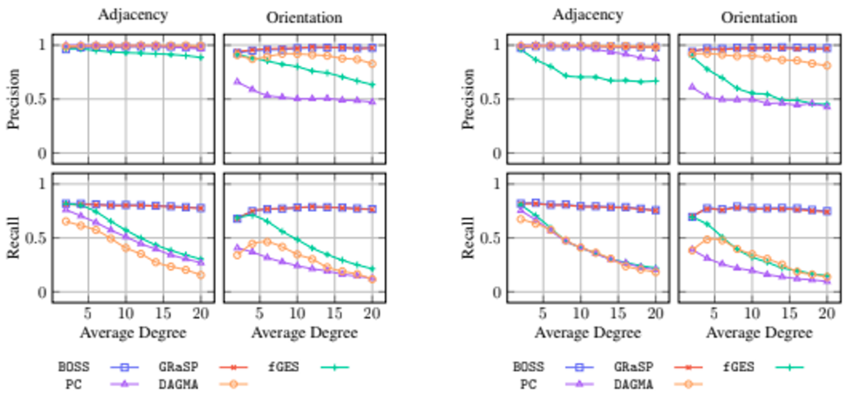
- FGES was used for adjacency search, which excels in scalability



Glasser et al., 2016

Challenge 7: High Connection Density

Accuracy can decrease for denser graphs



(a) Erdős-Rényi (b) Scale-free

Andrews et al. (under review)

- We applied FGES, which is highly scalable but can have lower performance for extremely dense graphs
- Better potential performance could be achieved using newer methods like GRaSP (Lam et al., 2022) or BOSS (Andrews et al., under review)

Challenge 8: Scale-Free Connectivity

- Rawls et al., (2022) reported nodes having greater-than-random connectivity, which is characteristic of scale-free networks

- Despite this, for densely connected hub nodes like ACC, methods like GRaSP might improve assessment of scale-free structure

BOSS returns scale-free connectivity

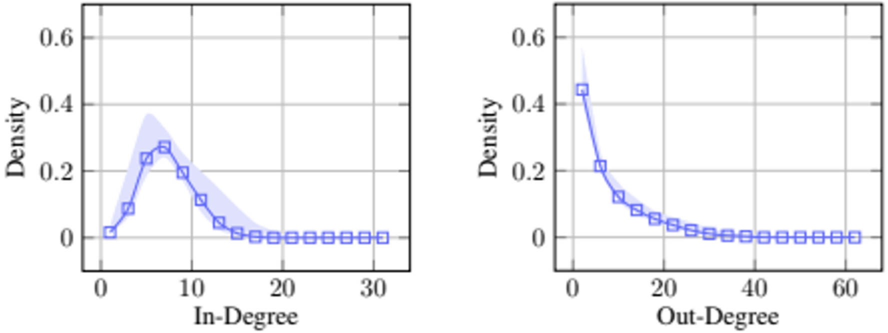
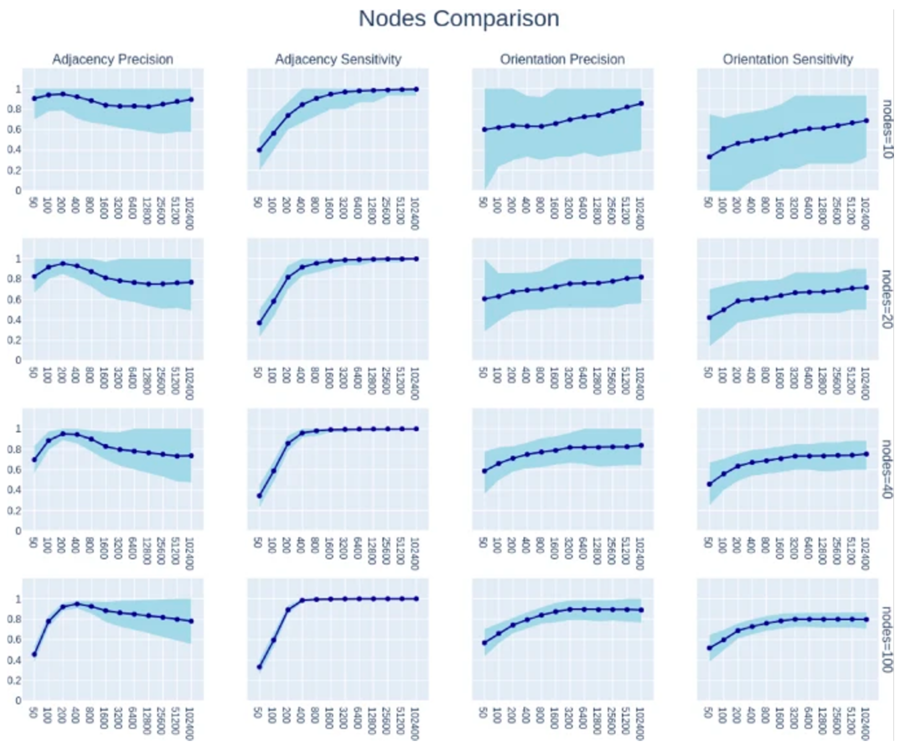


Figure 5: In/out-degree distributions on clinical resting state fMRI data.

Andrews et al. (under review)

Challenge 9: Limited Samples

- YA-HCP collected two sessions of 14:33 length each (2400 total volumes)
- We also applied CDA methods that have good small-sample performance
- However, many methods (e.g. ICA-LiNGAM) have higher sample size requirements, where this limitation is more likely to be an issue

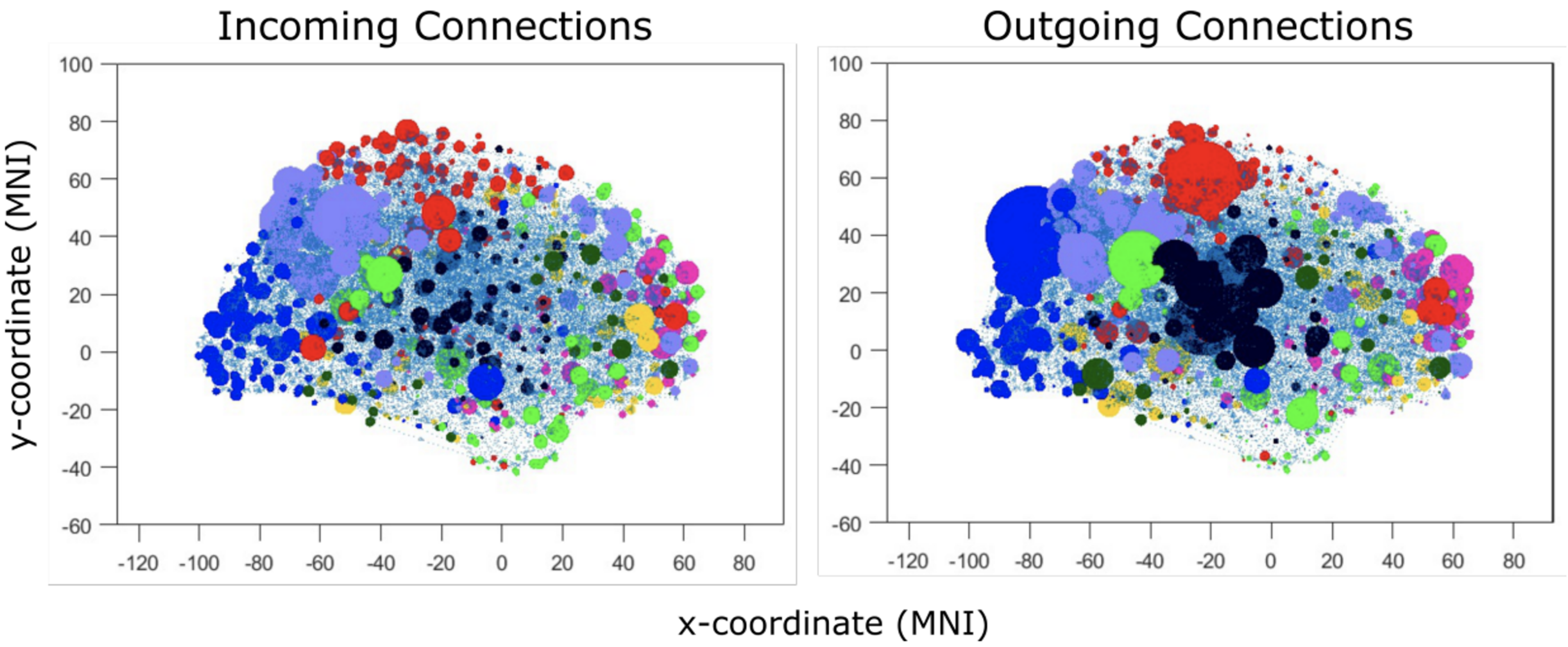


Kummerfeld et al., 2023

Case Study: Overall

- This recent large-scale application of CDA for deriving individualized causal connectomes addressed many of the challenges we identified.
- However, the challenges of high density and scale-free connectivity could potentially be better addressed by applying newer permutation-based CDA methods [Lam et al., 2022].
- Several challenges, such as limited samples, spatial smoothing, and preprocessing, were partially or entirely solved by the specific data set the method was applied to, and might pose problems in other data sets

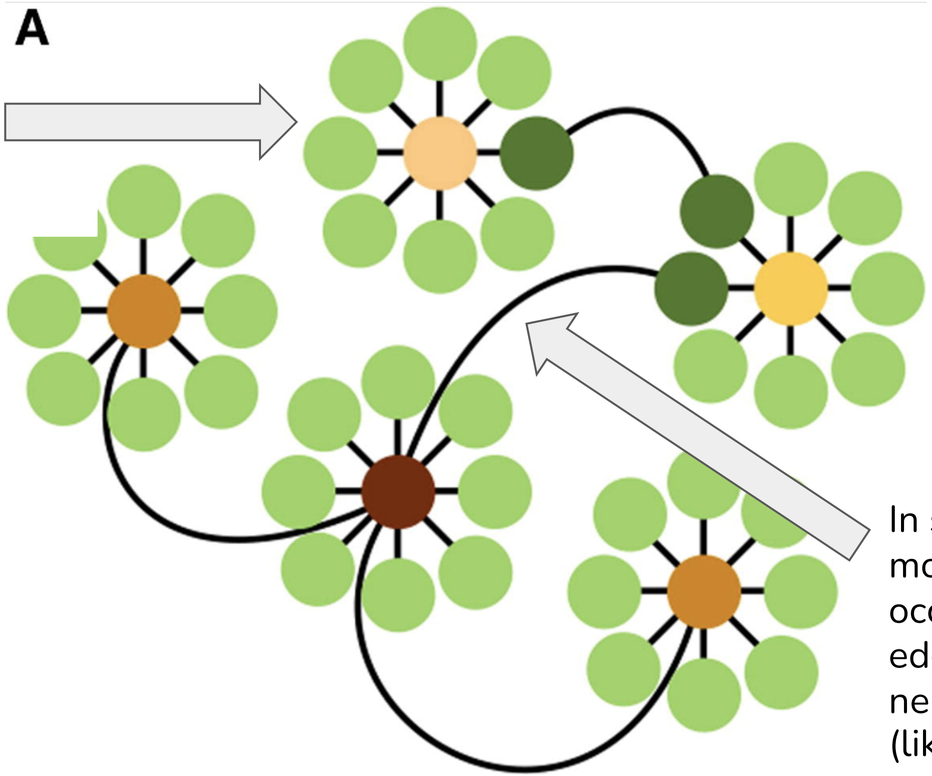
CASE STUDY RESULTS



GANGO Connectomes are Small-World Networks

What are “Small-World” Networks, and why are they Important?

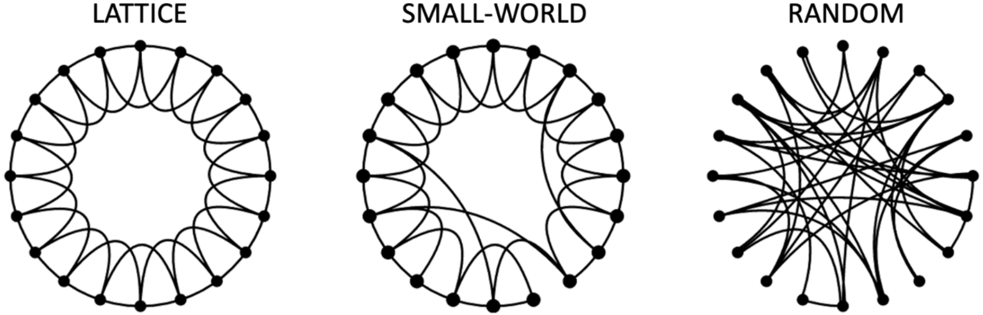
Small-world networks have a **modular structure** (these are tightly connected small neighborhoods)



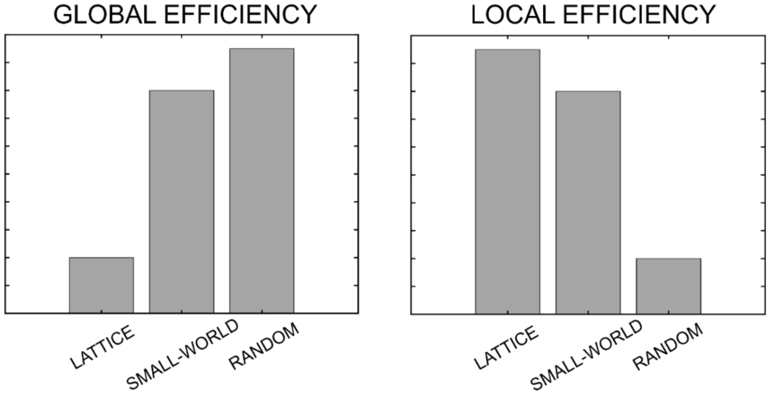
In small-world networks, modules are joined by occasional long-distance edges that link neighborhoods together (like highways)

Power et al., 2013

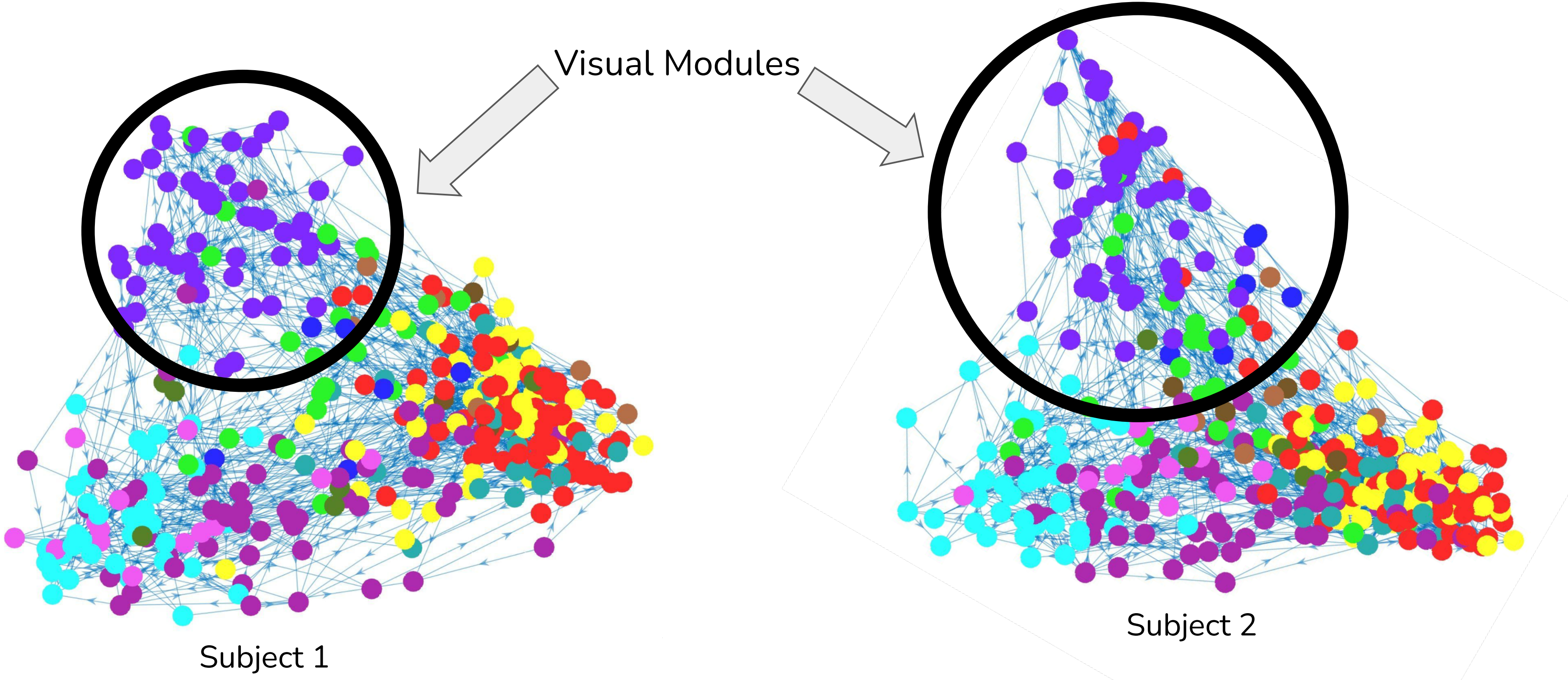
Small-World Networks



A biologically-plausible small-world network will have a global efficiency approaching that of a random graph, but a local efficiency higher than a random graph.

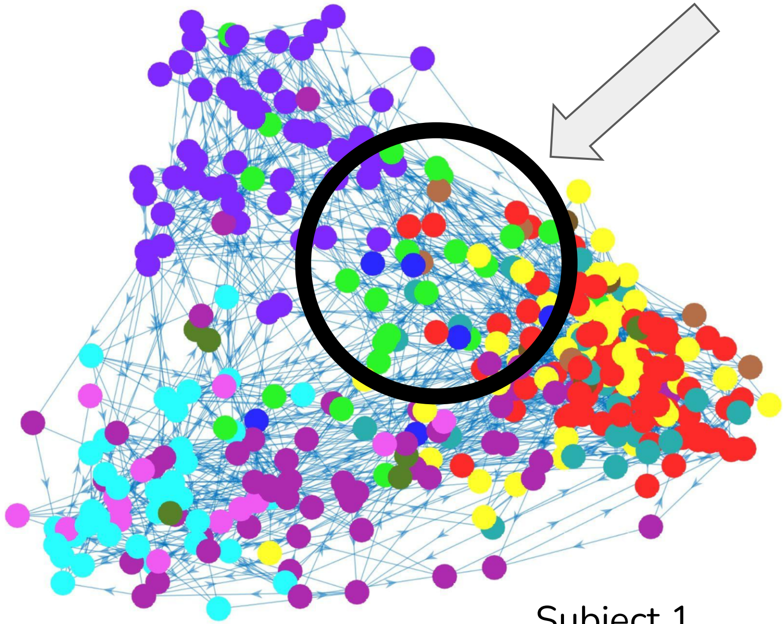


Causal Connectomes show Modular Network Structure

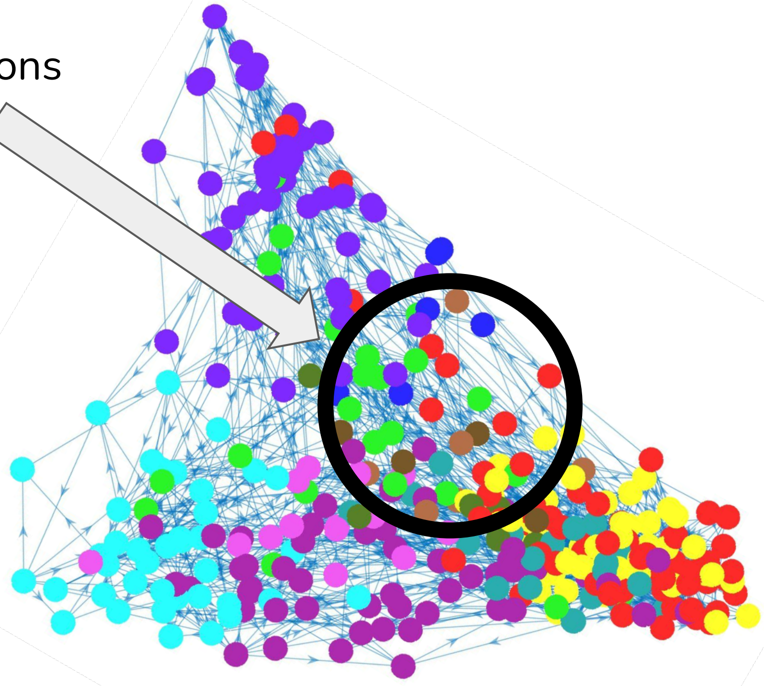


Causal Connectomes show Long-Distance Connections

Long-distance connections



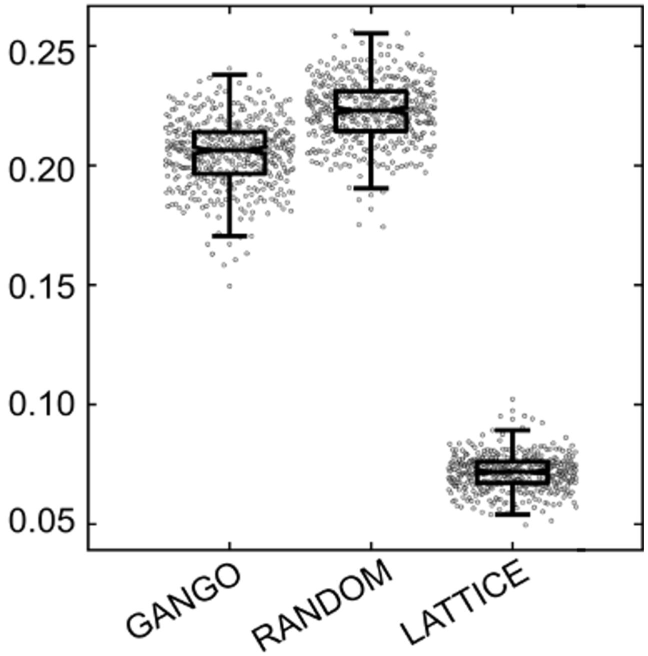
Subject 1



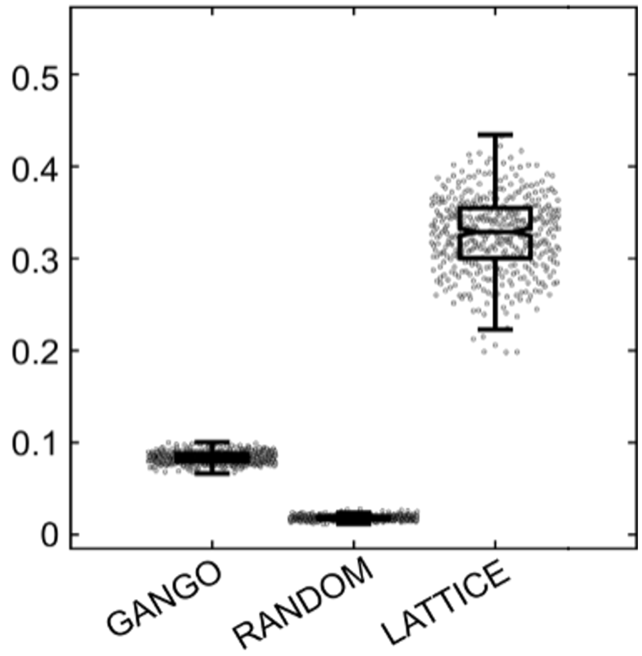
Subject 2

Causal Connectomes are Efficient Small-World Networks

GLOBAL EFFICIENCY



LOCAL EFFICIENCY



Causal Connectomes are Efficient Small-World Networks

Small-World Index
(Humphries & Gurney, 2008):

- **S = (Cg/Cr) / (Lr/Lg)**
- **S>1 = Small-World!**

Our measures:

$C_{GANGO} = 0.09$

$C_{RAND} = 0.02$

$L_{GANGO} = 0.21$

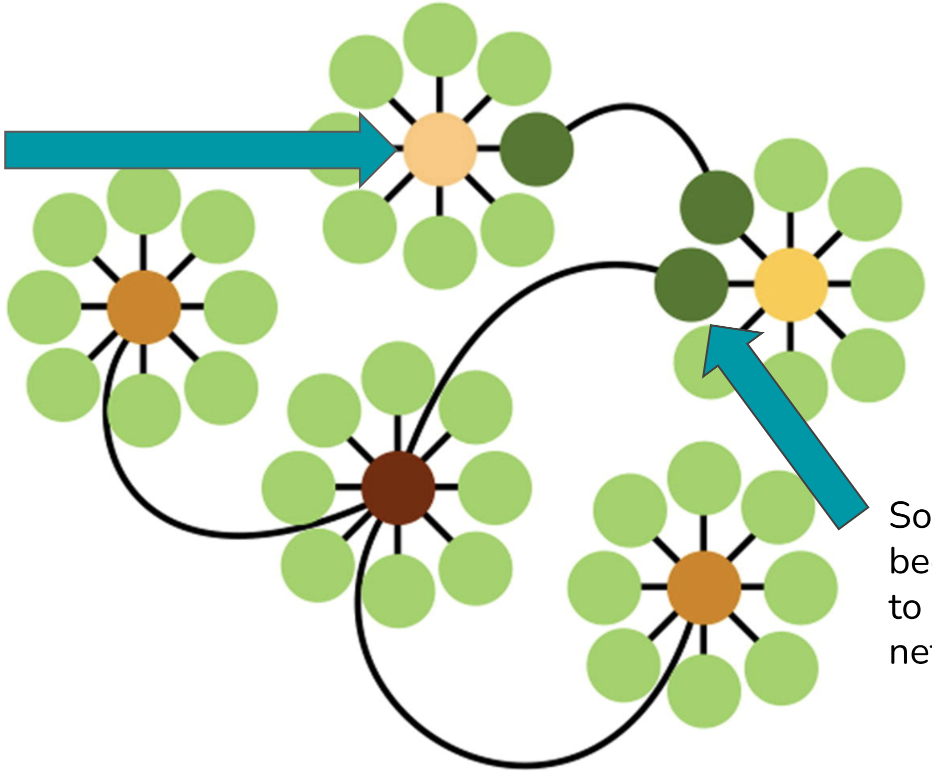
$L_{RAND} = 0.225$

$$S_{GANGO} = 4.2$$

GANGO Connectomes Show Scale-Free Connectivity

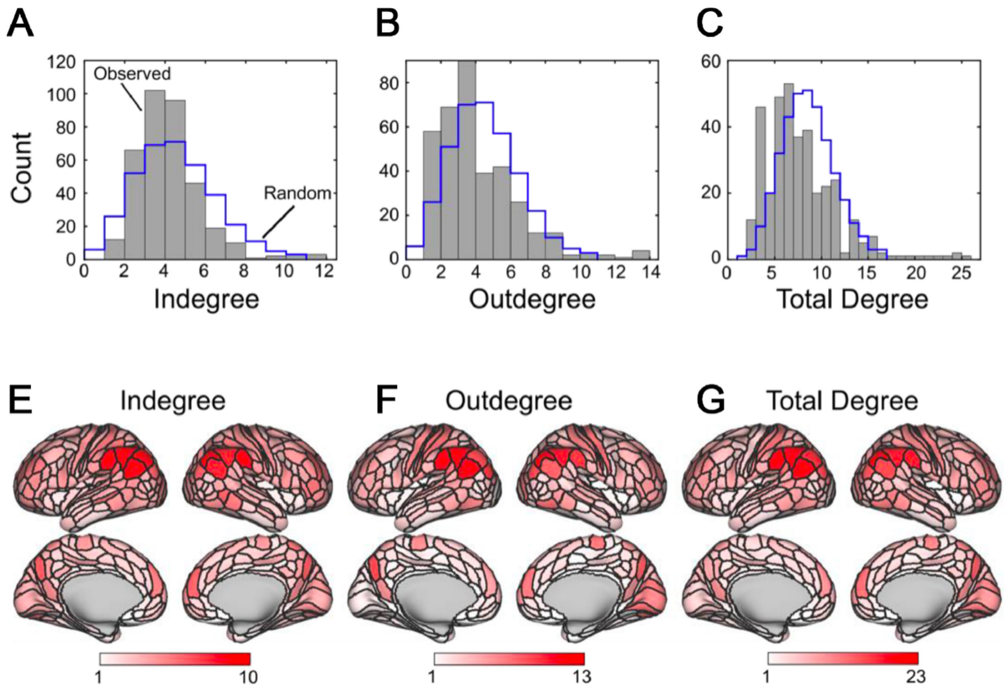
What are “Hubs” and why are they Important?

Some nodes are important because they have a large number of connections (**degree**)



Some nodes are important because they allow traffic to flow to other parts of the network (**betweenness**)

Scale-free Hubs of GANGO Connectomes



CDA Methods for Addressing these Challenges

	C1 Preprocessing	C2 Cycles	C3 Undersampling	C4 Latents	C5 Smoothing	C6 Dimensionality	C7 Density	C8 Scale-Free	C9 Samples
GES	✓	✗	✗	✗	✗	✓	✗	✗	✓
GRaSP	✓	✗	✗	✗	✗	∼	✓	✓	✓
Direct LiNGAM	∼	✗	✗	✗	✗	✓	✓	✓	✓
GANGO	∼	∼	✗	✗	✗	✓	∼	∼	✓
FASk	∼	✓	✗	✗	✗	✓	∼	∼	✓
Two-Step	∼	✓	✗	∼	✗	✓	∼	∼	✓

How 6 methods stand up to the 9 challenges.
✓ denotes the challenge is **addressed**.
∼ denotes the challenge is **partially addressed**.
✗ denotes the challenge is **not addressed**.

Limitations and Future Directions

- Gap 1: CDA methods for high-dimensional, high-density, scale-free models
- Gap 2: Reliance on skewed data
- Gap 3: Latent variables without giving up other challenges (e.g. cycles, high dimensionality, high density, etc.)
- Gap 4: Extension to other brain imaging technologies.

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