NeuroImaging Training Program

Functional Connectivity: Estimation and Inference with Markov Networks

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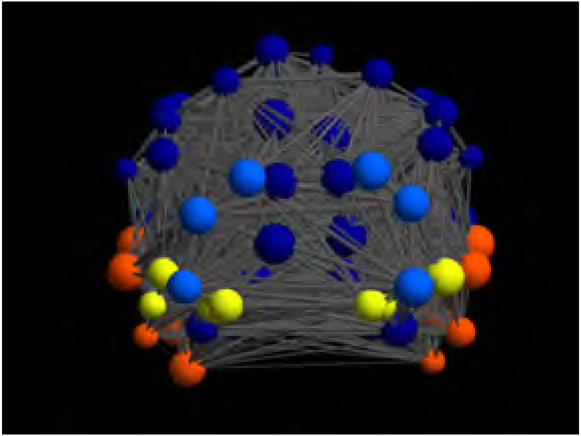
1. Functional Connectivity
2. Markov Networks
   - What are Markov Networks?
3. Estimating Functional Connections
4. Population Inference
   - Case Study: Neural Networks of Synesthesia

Functional Connectivity

Statistically estimated relationships between regions in the brain.



From fMRI to Functional Connectivity

1. Standard fMRI Pre-processing.
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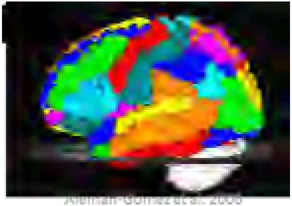
   - Anatomical: Harvard-Oxford, AAL, Talairach, etc.



Aleman-Gomez et al. 2006

   - Functional regions: Power et al., 2012, Craddock et al., 2012, etc.

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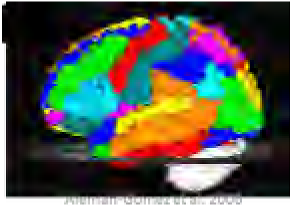
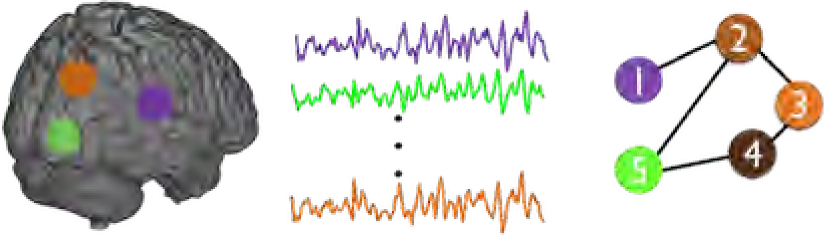


   - Functional regions: Power et al., 2012, Craddock et al., 2012, etc.
3. $\mathbf{X}$ a $p \times T$ matrix of p ROIs by T time points the input to a network estimation procedure.

From fMRI to Functional Connectivity

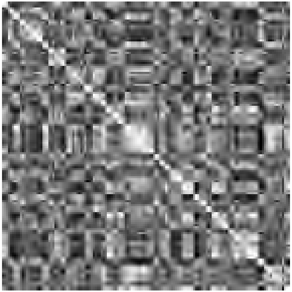


Networks fit to the time series of each ROI.

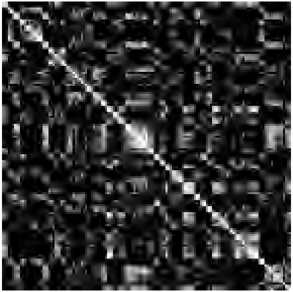
Nodes: Brain regions (ROIs).
Edges: Estimated connections between regions.

What model for connectivity?

1. **Correlation**.



Correlation matrix between brain regions.



Thresholded correlation matrix.

2. Granger causality.

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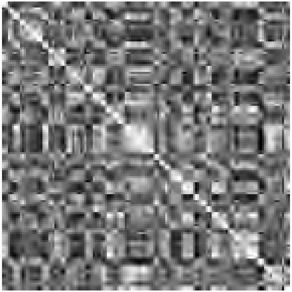

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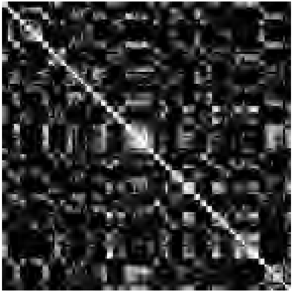

Thresholded correlation matrix.

2. Granger causality.
3. Partial Correlation.
   - Equivalent to **Markov Networks** for Gaussian data (fMRI).

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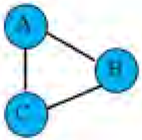
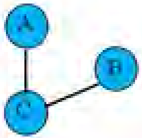
Markov Networks

Markov Network

An *undirected graphical model* that characterizes conditional dependence (direct) relationships.



- *Edge*: Two brain regions are **conditionally dependent**.
- *No edge*: Two brain regions are **conditionally independent**.



$$A \perp B \mid C$$

Markov Networks - Conditional Dependence

Regression Interpretation:

- Imagine trying to predict the time series in Region A (response) by the time series of all other brain regions (predictors).

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  - Edge.

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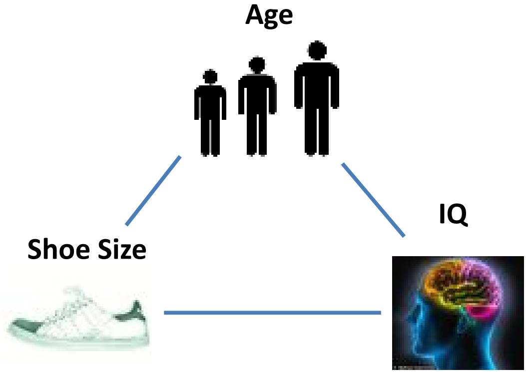
Regression Interpretation:

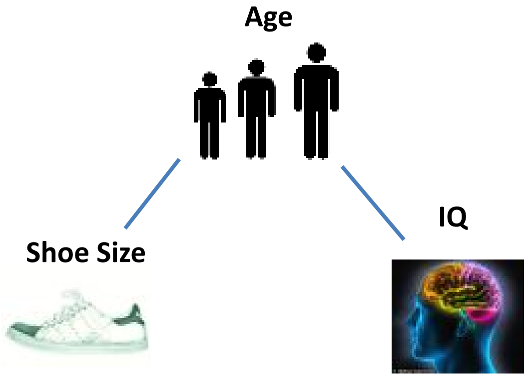
- Imagine trying to predict the time series in Region A (response) by the time series of all other brain regions (predictors).
- Region B predictive of Region A (with all other regions in model).
    - A is conditionally dependent on B.
    - Edge.
- Because of other regions in model, Region B does not add any predictive value for Region A.
    - A is conditionally independent on B.
    - No Edge.

Markov Networks - Conditional Dependence



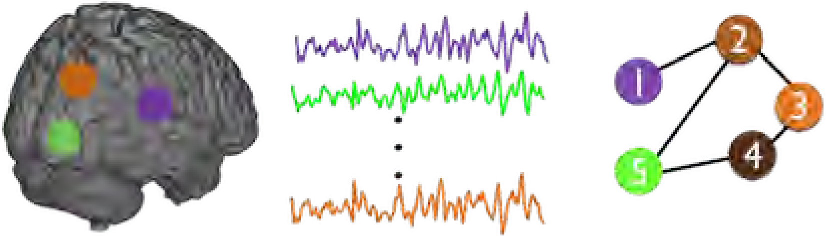
Correlation.

Markov Networks - Conditional Dependence



Conditional Dependence (Partial Correlation).

Why Markov Networks for Functional Connectivity?



1. Biological and Clinical interpretability of **direct functional connections**.
2. Robust to physiological confounds (motion!). [Smith et al., 2011; Craddock et al., 2013]

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Gaussian Graphical Models

- Multivariate normal: $\mathbf{X} \sim N(0, \mathbf{\Omega}^{-1})$
- $\mathbf{\Omega}$ the inverse covariance matrix (partial correlation).
- Zeros in $\mathbf{\Omega} \implies$ conditional independence!
  - Edges correspond to non-zeros in $\mathbf{\Omega}$.

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Estimate sparse $\mathbf{\Omega}$ via Penalized Maximum Likelihood Estimation (MLE).

Graphical Lasso (Glasso)

$$\underset{\mathbf{\Omega}}{\text{maximize}} \quad \log|\,\mathbf{\Omega}\,| - \text{tr}(\mathbf{X}^T\mathbf{X}\,\mathbf{\Omega}) - \lambda||\,\mathbf{\Omega}\,||_1$$

- Blue: Log-likelihood.
- Red: Penalty that encourages zeros in $\mathbf{\Omega}$.

[d'Aspremont et al., 2006; Friedman et al., 2008; Meinshausen and Buhlmann, 2006; and many others]

Network Sparsity

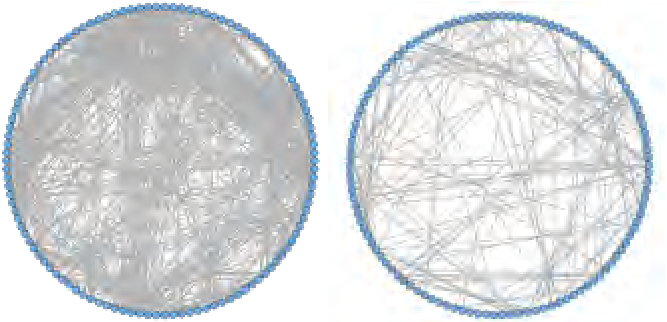
λ Controls Sparsity.

$$\underset{\mathbf{\Omega}}{\text{maximize}} \quad \log|\,\mathbf{\Omega}\,| - \text{tr}(\mathbf{X}^T\mathbf{X}\,\mathbf{\Omega}) - \lambda||\,\mathbf{\Omega}\,||_1$$

- $\lambda = 0$ gives a dense network (no sparsity).
- As λ increases, network becomes more sparse.

- Modulates trade-off between model fit and network sparsity.

Network Sparsity



Estimated Networks at different λ values - UCLA ABIDE Data Set

How to Choose λ?

Stability Selection.

- Idea: Choose λ that gives the most **stable network**.

Procedure:

1. Repeatedly resample (bootstrapping or sub-sampling) time points.
2. Choose λ that results in the smallest network variability across resamples.
3. *Stability Score*: For each edge, the proportion of resamples in which edge was selected.

Mimics repeated fMRI scanning / test-retest scanning.

[Meinshausen & Buhlmann, 2011 and Liu et al., 2011]

Whitening the Time series

Recall: $\mathbf{X}$ is our $p \times T$ matrix of ROIs by time points.

Question: Should we input $\mathbf{X}$ into Glasso procedure?

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Question: Should we input $\mathbf{X}$ into Glasso procedure?

NO!

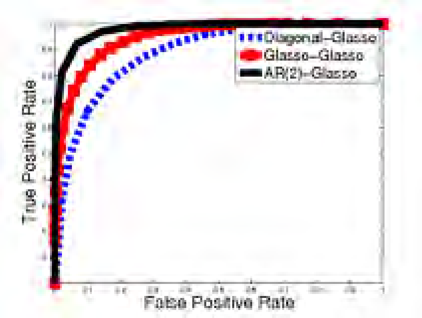
Why?

- Glasso assumes observations are independent.
- fMRI time series are correlated.
  - **Auto-regressive (AR) process** [Worsley et al., 2002]

Whitening the Time series

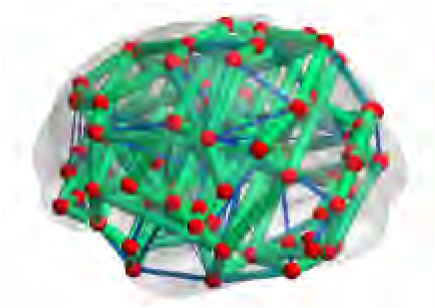
Solution:

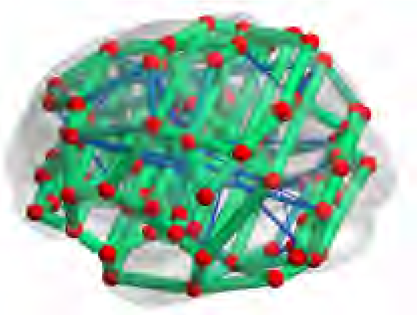
1. Fit AR model to time series.
2. Use model to **whiten** time series.



Simulation from Narayan et al., 2014.

Estimated Functional Connections for Synesthesia Study





Control Network (Left; 19 subjects) and Synesthesia (Right; 20 subjects) [Tomson et al., 2013; Narayan et al., 2014]

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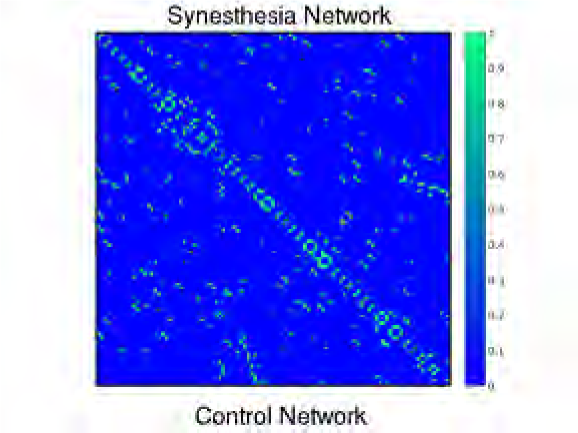

[Tomson et al., 2013; Narayan et al., 2014]

MoNet: Markov Network Toolbox for Functional Connectivity

Available from `http://www.stat.rice.edu/~gallen/` or `https://bitbucket.org/gastats/monet/overview`.

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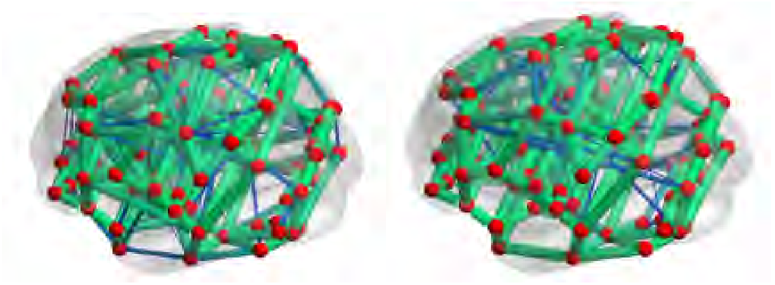
Population Inference for Functional Connectivity

How do functional connections differ between two populations of subjects?



Control Network (Left; 19 subjects) and Synesthesia (Right; 20 subjects)
[Tomson et al., 2013; Narayan et al., 2014]

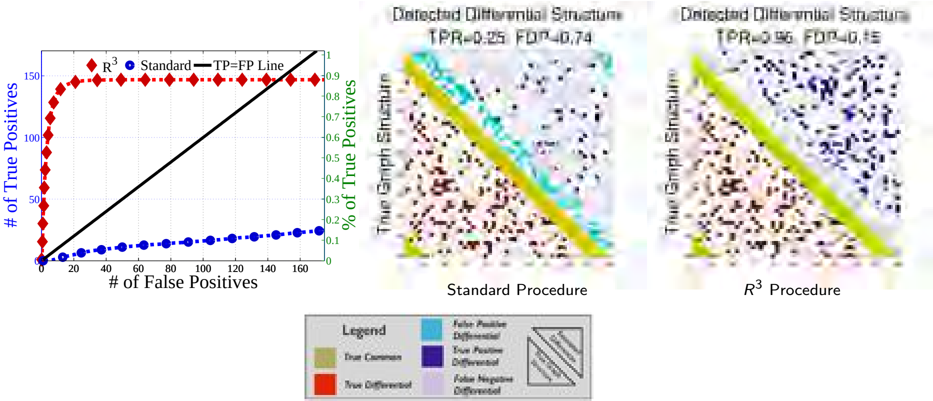
Goal: Want to find **Statistically Significant** network differences.

Standard Approach to Inference

1. Estimate a network for each subject.
2. Aggregate graph metrics across subjects.
   - Edges, degree, clustering coefficient, participation coefficient, global sparsity, etc.
3. Use two-sample T-tests (or Wald tests).
   - Permutation nulls.
4. Correct for multiple testing.

[Bullmore and Sporns, 2009; Palaniyappan et al., 2013; Tao et al., 2013; Zalesky et al., 2010]

Standard Approach to Inference



Simulation from Narayan et al., 2014.

What went wrong?

1. Two-levels of Network Variability.
   - Subject networks are estimated.
   - Estimated quantities are random variables!

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Subject networks are not measured data, but statistically estimated quantities.

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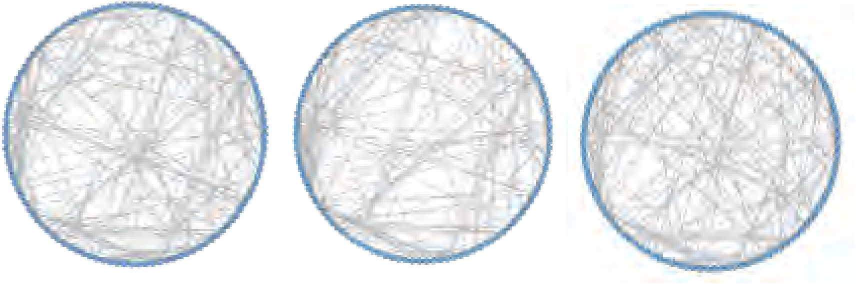
Subject networks are not measured data, but statistically estimated quantities.

2. Graph Selection Errors.
   - Errors at the subject level can propagate and confound inference at the population level.

Two-Levels of Network Variability

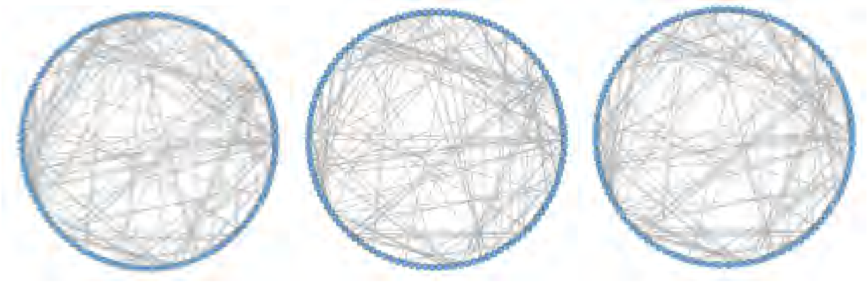
Between Subject Variability:



3 Control Subjects from UCLA ABIDE Data Set

Two-Levels of Network Variability

Network Variability within a Single Subject:



3 Estimated Networks after Resampling - Control Subject from UCLA ABIDE Data Set

Our Approach: R^3

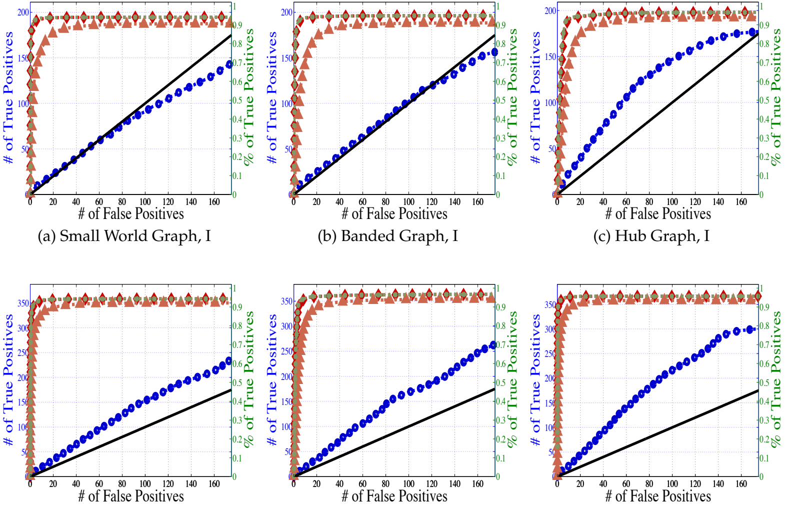
R^3 Procedure:

- *Resampling*. Bootstrapping to estimate subject network variability.
- *Random Effects*. Correct test statistics that account for two-levels of variability.
- *Random Penalization*. Improves errors associated with graph selection.

Higher statistical power and improved error control.

Our Approach: R^3

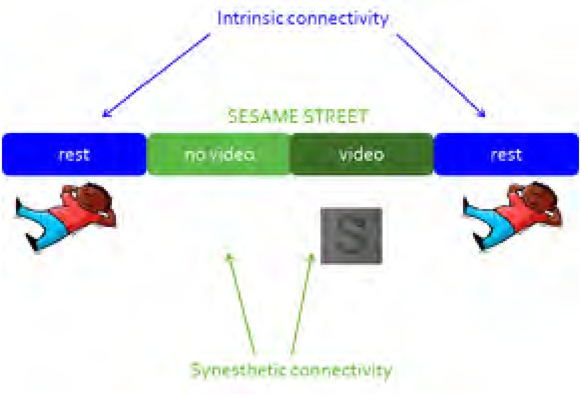
Simulation Study - ROC Curves:



(a) Small World Graph, I (b) Banded Graph, I (c) Hub Graph, I

(d) Small World Graph, II (e) Banded Graph, II (f) Hub Graph, II

Case Study: Color-Sequence Synesthesia

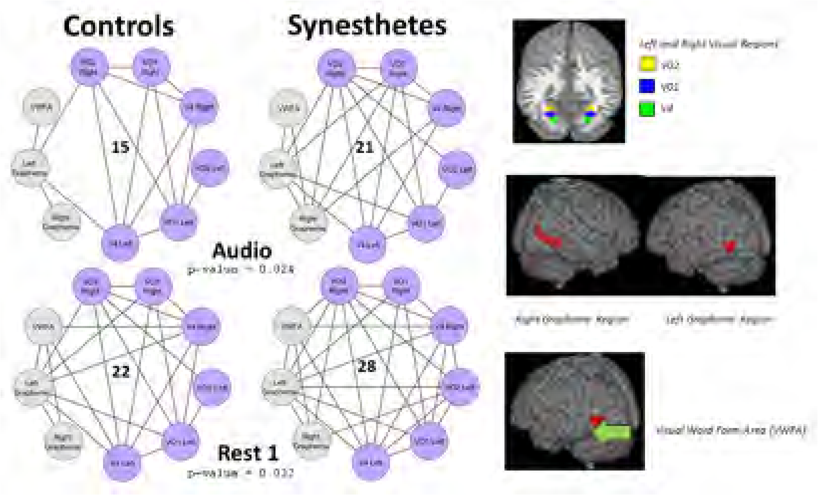


- Experiment: 20 Synesthetes and 19 Controls were scanned while resting, listening to Sesame Street (but no video), watching Sesame Street, and then resting again.

(Tomson et al., 2013)

Case Study: Color-Sequence Synesthesia

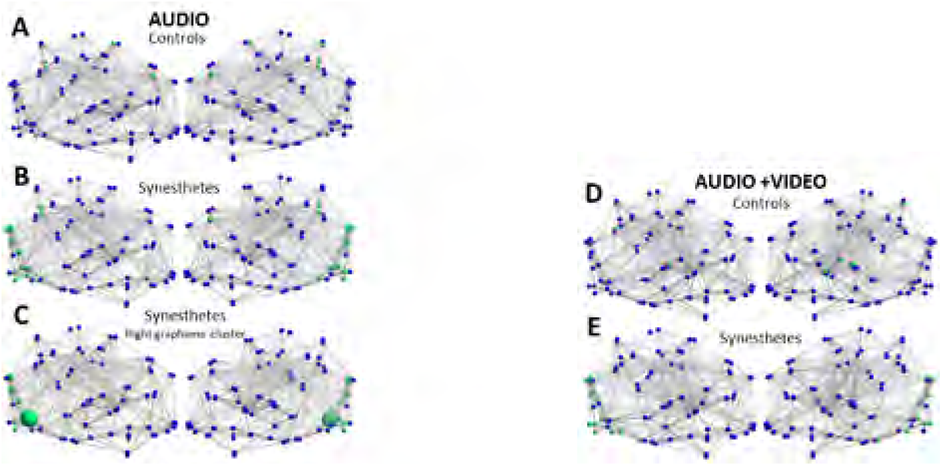
Global Differences: Sparsity Levels



Brain regions that process color have more connections to those that process numbers and letters in synesthetes than controls.

Case Study: Color-Sequence Synesthesia

Are there different node clustering patterns between the two groups?



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Technical Message - Inference

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- Manjari Narayan, PhD Candidate, Electrical and Computer Engineering, Rice University.

References

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