A computational framework for analysis of functional MRI data for developing imaging-derived biomarkers for HIV Associated Neurocognitive Disorders

PhD Thesis Proposal

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Proposed research

- Computational approach for analysis of functional MRI data
- Focus on improved characterization of information flow within the brain
- Network analysis approaches for identifying changes in the brain during neurologic diseases
- Study of HIV Associated Neurocognitive disorders

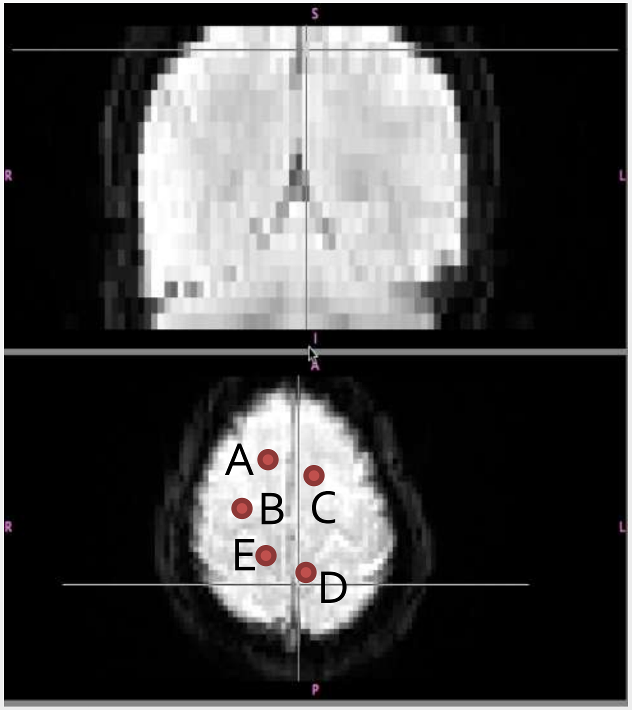
Functional Magnetic Resonance Imaging (fMRI)

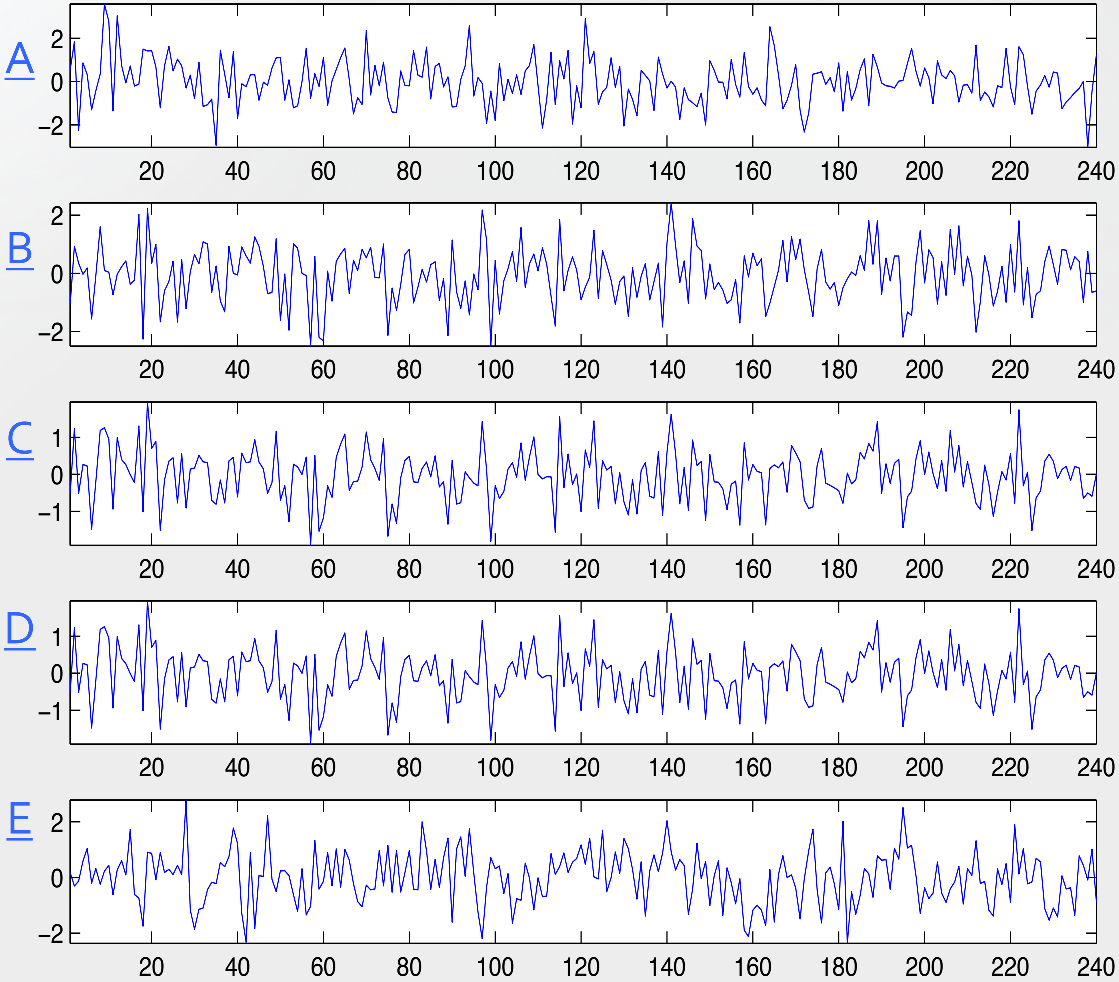
- A technique for measuring brain activity over time using MRI

- Detects the changes in oxygenated blood flow, hence referred to as BOLD fMRI

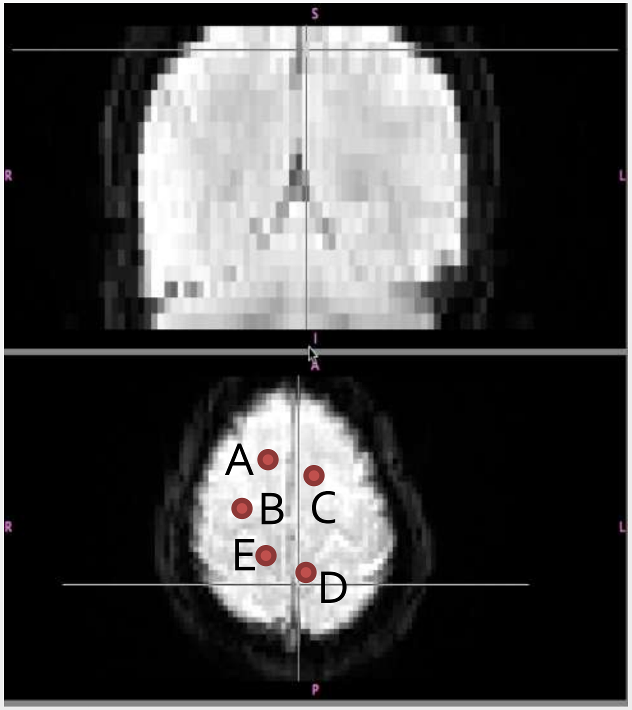
- Resting state fMRI without any stimulus has been used to capture explicit patterns in brain activity
- Reproducible resting state networks have been observed

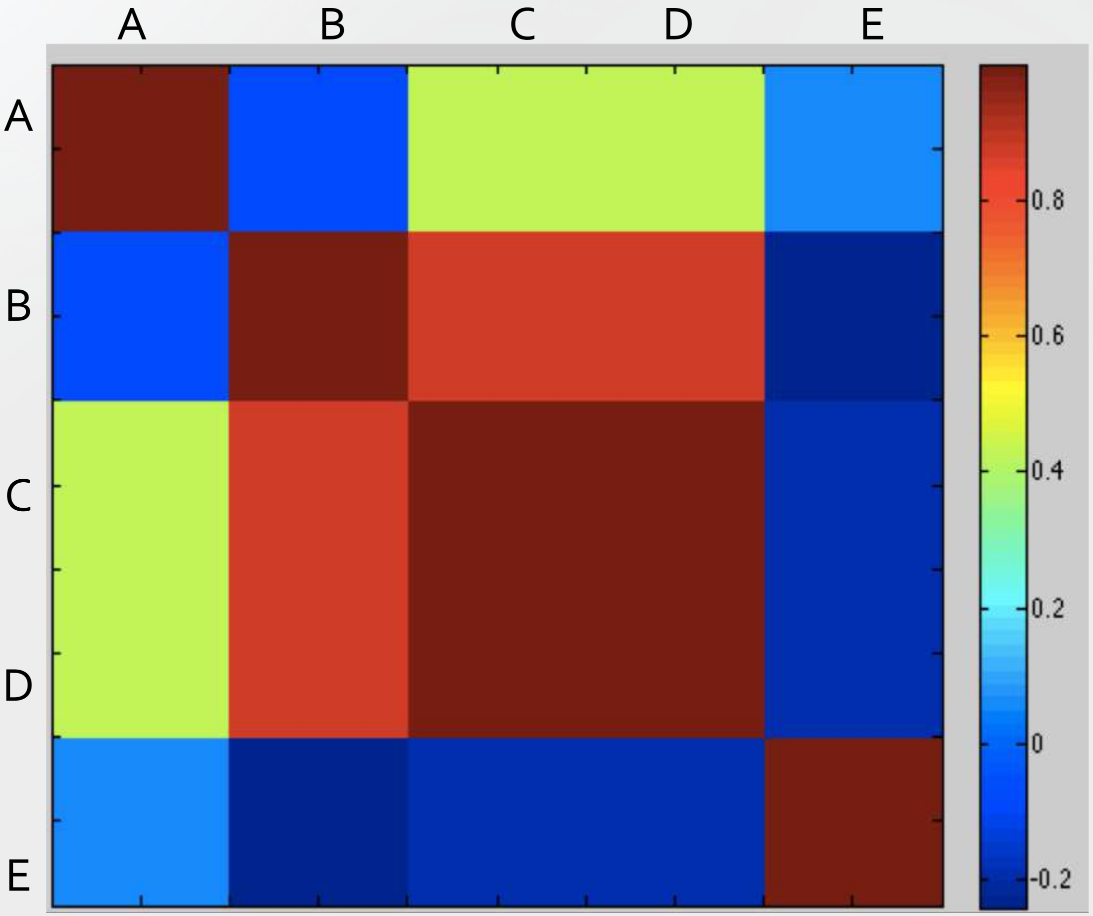
fMRI time series





fMRI time series



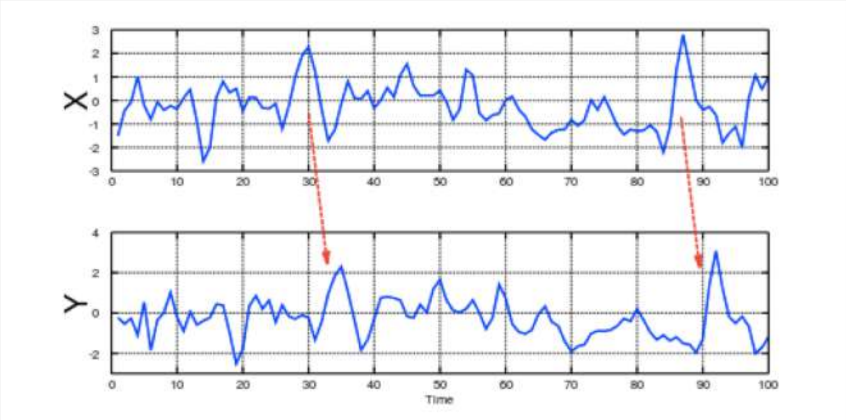


Information Theory and Causality

- Methods in information science enable us to quantify the information flow between such time series

- Can one time series be helpful in forecasting another?

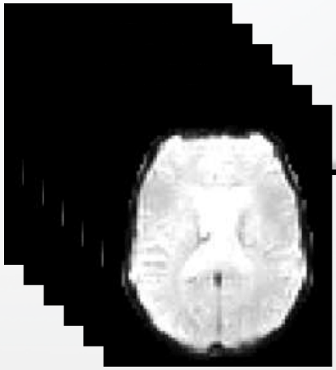
- Measuring such a prediction ability indicates the presence of a directional influence



HIV Associated Neurocognitive Disorder (HAND)

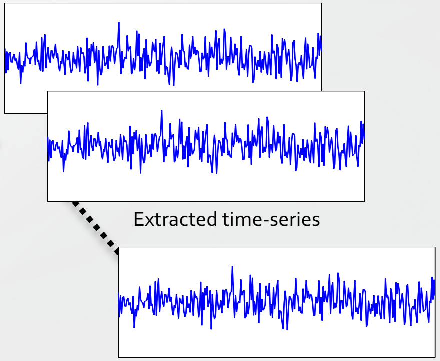
- Reports estimate that about 1.2 million Americans and 40 million people worldwide live with HIV/AIDS
- HIV is capable of invading the brain soon after seroconversion and causing continuous neuronal injury
- Can eventually lead to deficits in multiple cognitive domains commonly referred to as HIV-associated neurocognitive disorders (HAND)
- Difficult to detect, particularly when mild impairment persists

Outline



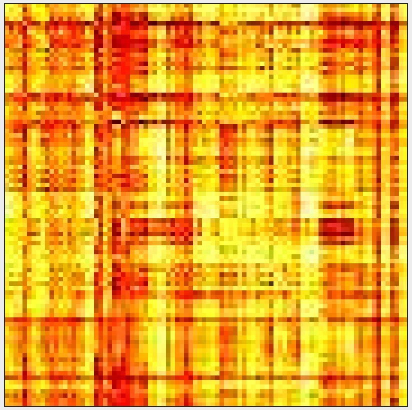
4D fMRI data

Preprocessing

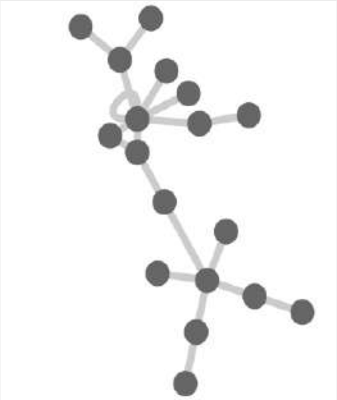


Extracted time-series

Directed Connectivity

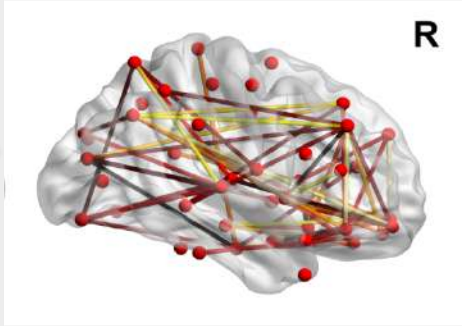


Network Analysis



Statistical Analysis

Study of HIV Associated Neurocognitive Disorder



Specific Aims

1. **To develop and evaluate novel time-series analysis methods for exploring connectivity in high-dimensional time-series ensemble.**
    - Develop the framework utilizing state-space reconstruction and radial basis function networks, for capturing non-linear pair-wise interactions in time-series.
    - Explore the applicability of multivariate time-series analysis methods for recovery of underlying network interactions using large-scale Granger causality.
    - Systematically test and evaluate the performance of the methods for adequate recovery of underlying network structure via the use of benchmark datasets and functional MRI simulations.

Approach - Connectivity

- Existing methods have certain disadvantages owing to *a priori* assumptions, linear models
- Can the use of non-linear techniques enhance the characterization of connectivity?
- Mutual Connectivity Analysis using Generalized Radial Basis Function network (MCA-GRBF)

Approach - Connectivity

- According to dynamical systems theory, the state of a system at every instant is controlled by its state variables
  - Two time-series are causally linked if they share a common state space

- fMRI time-series are not the actual state variables, but only a projection on a lower dimensional space

- Interactions can be better understood using state-space reconstruction
  - A time-delayed sequence of observations can be used to represent/understand the original state-space of systems

Approach - Connectivity

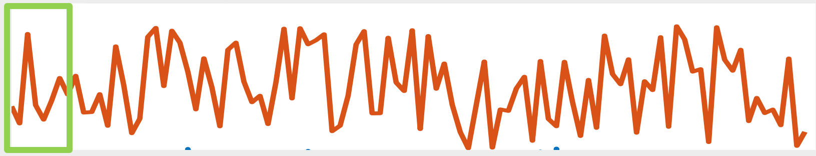
- We can construct a *d*-dimensional state space

For a given time-series, say $x(t)$

$$\mathbf{x}_t = \Big(x\big(t\big), x\big(t+1\big), \ldots, x\big(t+d\big)\Big),\; t = 1, 2, \ldots, l-d\,,$$

where, d is the embedding dimension

& l is the length of the time-series



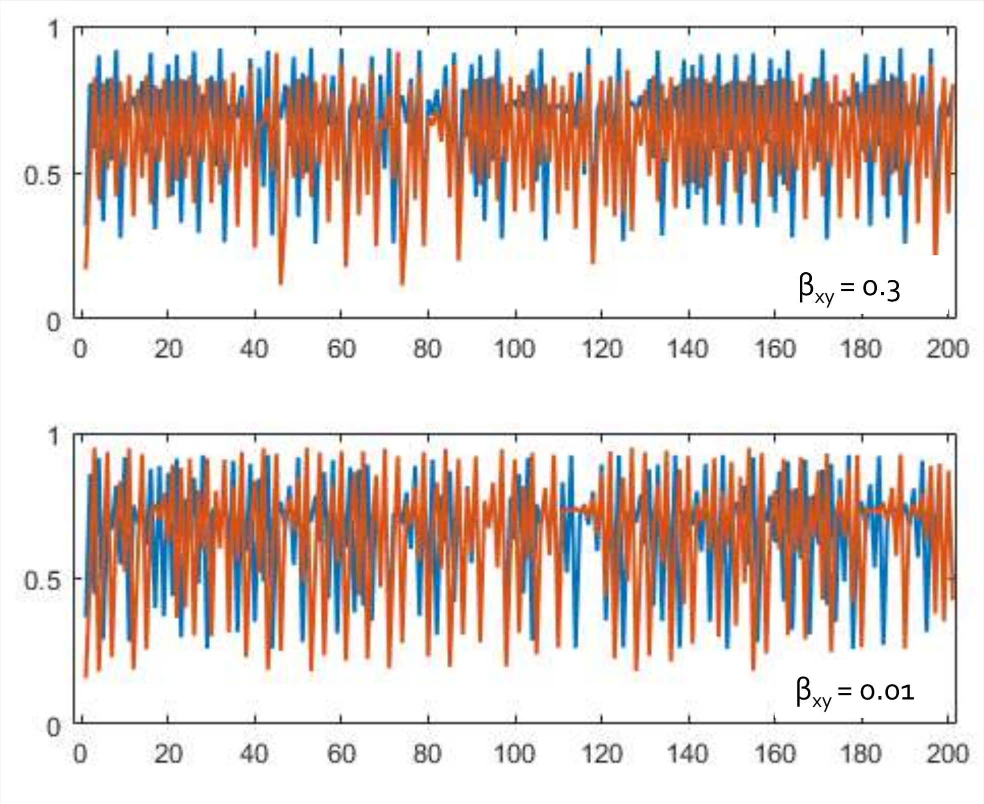
- Exact embedding dimensions of a system are not known but can be estimated quantitatively (Cao's criterion)

Approach - Connectivity

Lotka-Volterra 2 species models*

$$x(t+1) = x(t)(r_x - r_x x(t) - \beta_{xy} y(t))$$
$$y(t+1) = y(t)(r_y - r_y y(t) - \beta_{yx} x(t))$$

where, $r_x = 3.7, r_y = 3.8, \beta_{yx} = 0.01$



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*Sugihara, G., May, R., Ye, H., Hsieh, C. H., Deyle, E., Fogarty, M., & Munch, S. (2012). Detecting causality in complex ecosystems. *science*, *338*(6106), 496-500
Ma, H., Aihara, K., & Chen, L. (2014). Detecting causality from nonlinear dynamics with short-term time series. *Scientific reports*, *4*.

Approach - Connectivity

Lotka-Volterra 2 species models

$$x(t+1) = x(t)(r_x - r_x x(t) - \beta_{xy} y(t))$$
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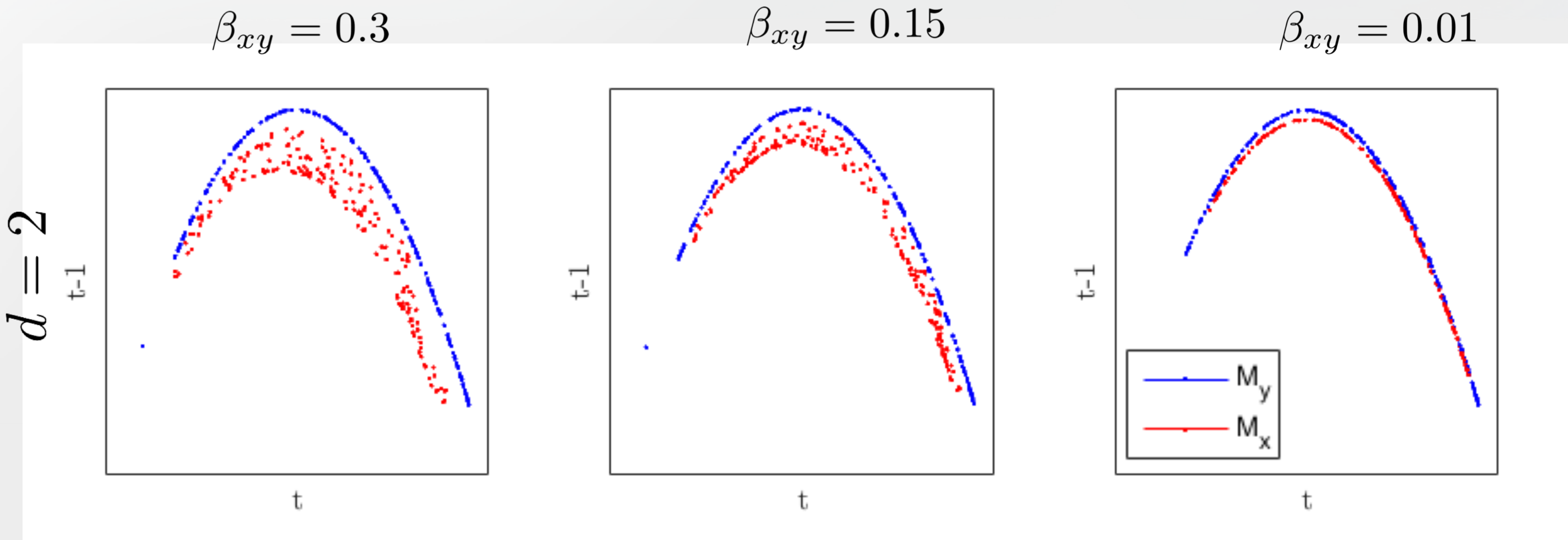
where, $r_x = 3.7, r_y = 3.8, \beta_{yx} = 0.01$

$\beta_{xy} = 0.3$ $\beta_{xy} = 0.15$ $\beta_{xy} = 0.01$



Approach - Connectivity

Lotka-Volterra 2 species models

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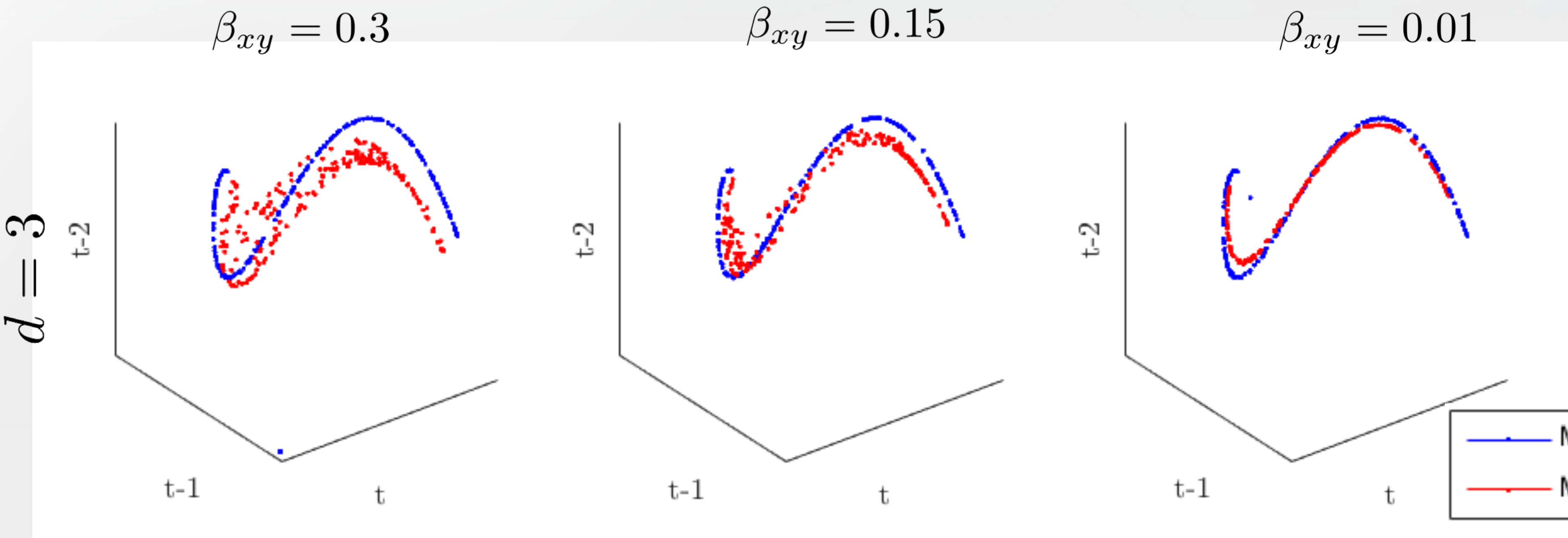
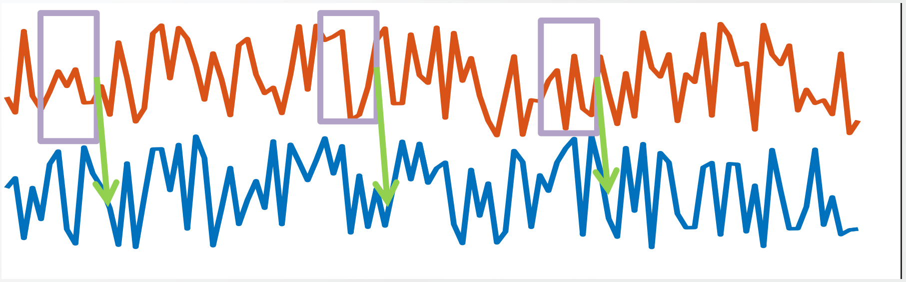


Approach - Connectivity

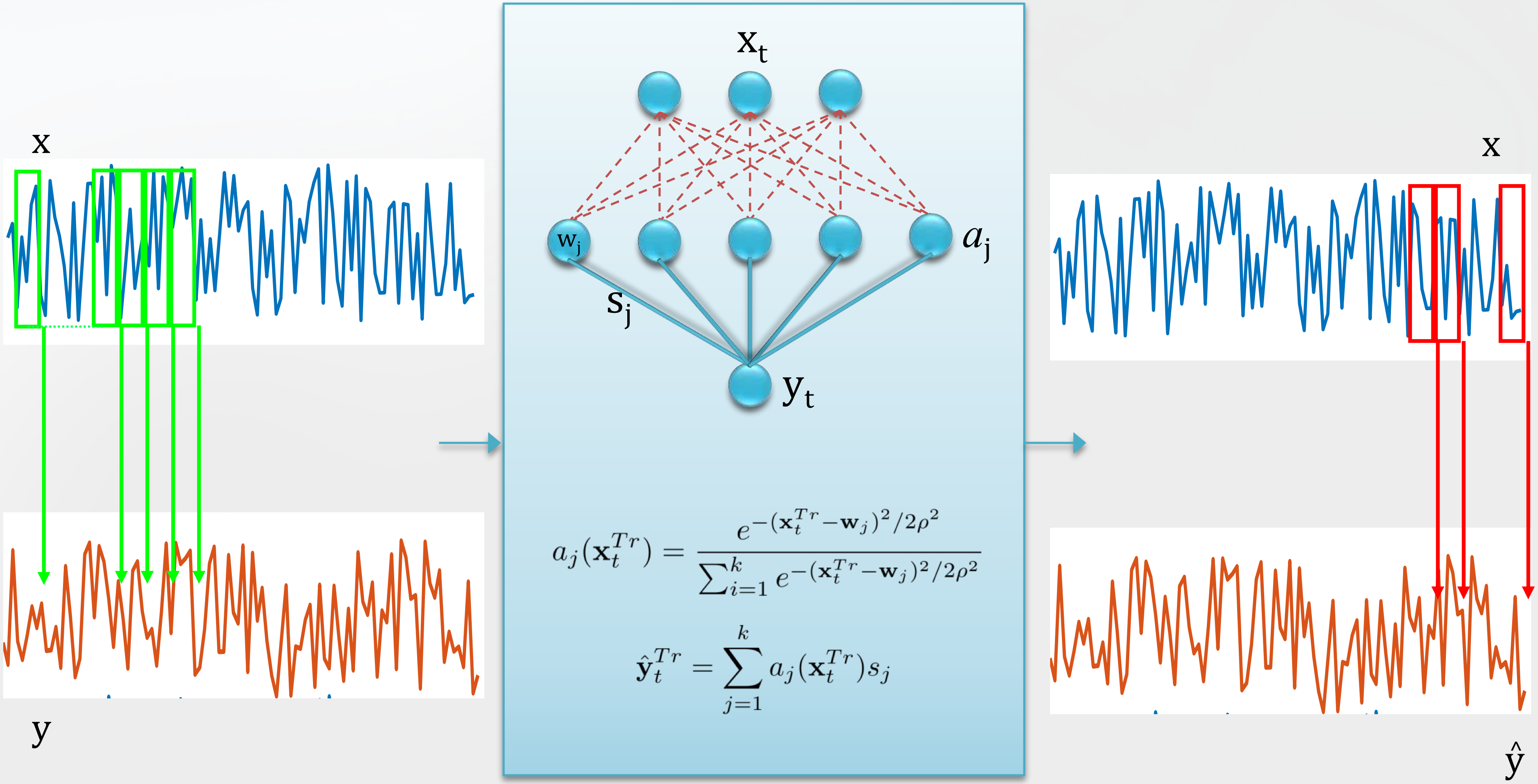


$$\mathbf{y}_t = f(\mathbf{x}_t)$$

- Using a radial basis function neural network (Mutual Connectivity Analysis *)
- An input, hidden and output layer
- Can the past of $\mathbf{x}$ be used to predict/cross-map a future $\mathbf{y}$

Wismüller, A., Abidin, A. Z., et al. (2016). Mutual Connectivity Analysis (MCA) for Nonlinear Functional Connectivity Network Recovery in the Human Brain Using Convergent Cross-Mapping and Non-metric Clustering. In *Advances in Self-Organizing Maps and Learning Vector Quantization* (pp. 217-226). Springer, Cham.

Approach – MCA GRBF



$$a_j(\mathbf{x}_t^{Tr}) = \frac{e^{-(\mathbf{x}_t^{Tr}-\mathbf{w}_j)^2/2\rho^2}}{\sum_{i=1}^{k} e^{-(\mathbf{x}_t^{Tr}-\mathbf{w}_j)^2/2\rho^2}}$$

$$\hat{\mathbf{y}}_t^{Tr} = \sum_{j=1}^{k} a_j(\mathbf{x}_t^{Tr}) s_j$$

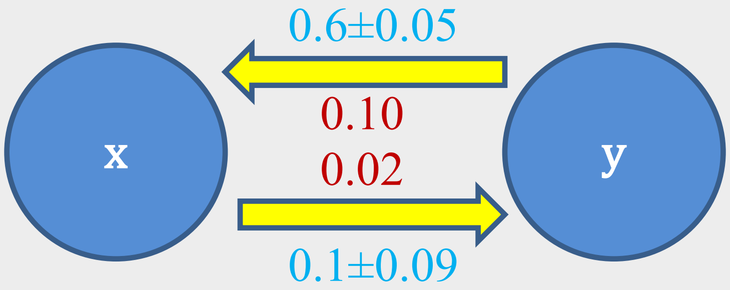
$$M_{\mathbf{y}\rightarrow\mathbf{x}} = corr(\mathbf{y},\hat{\mathbf{y}})$$

Validation(s)

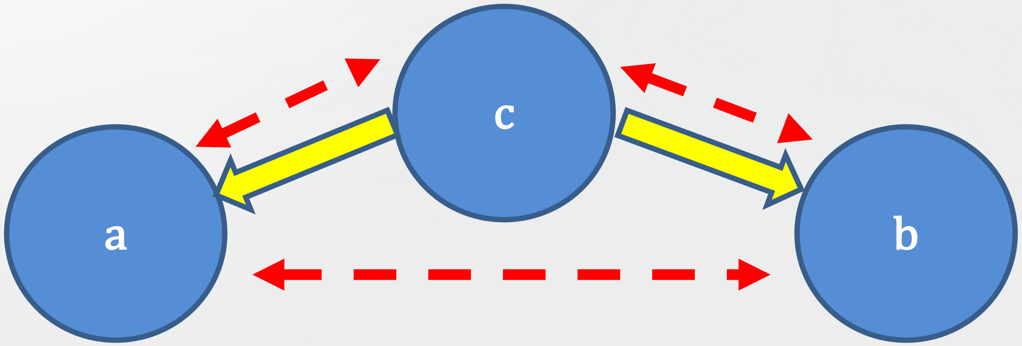
Lotka-Volterra 2 species models

$$x(t+1) = x(t)(r_x - r_x x(t) - \beta_{xy} y(t))$$
$$y(t+1) = y(t)(r_y - r_y y(t) - \beta_{yx} x(t))$$

where, $r_x = 3.7, r_y = 3.8$



Indirect interactions

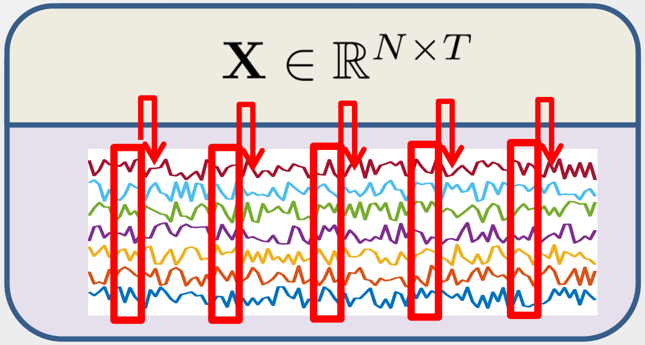


Granger Causality

Vector Auto-Regressive (VAR) Modelling

Consider a system, $\mathbf{X}$, with N time series.

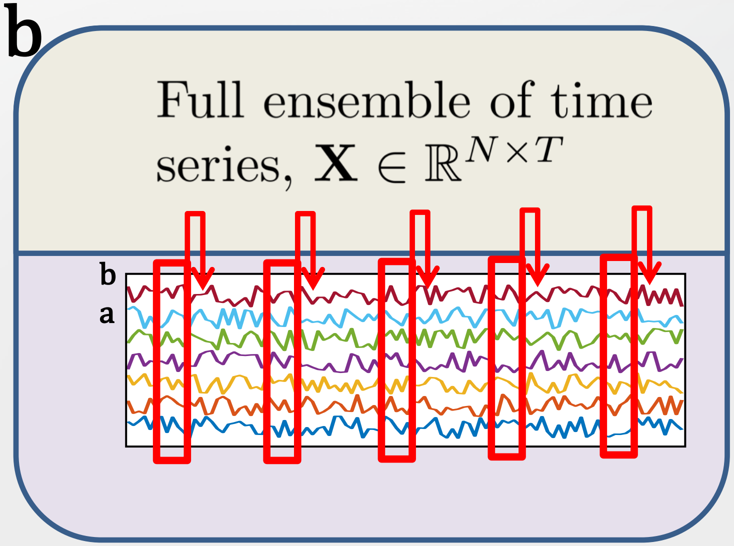
$$x(t) = \sum_{j=1}^{m} \mathbf{AR}_j x(t-j) + e(t)$$



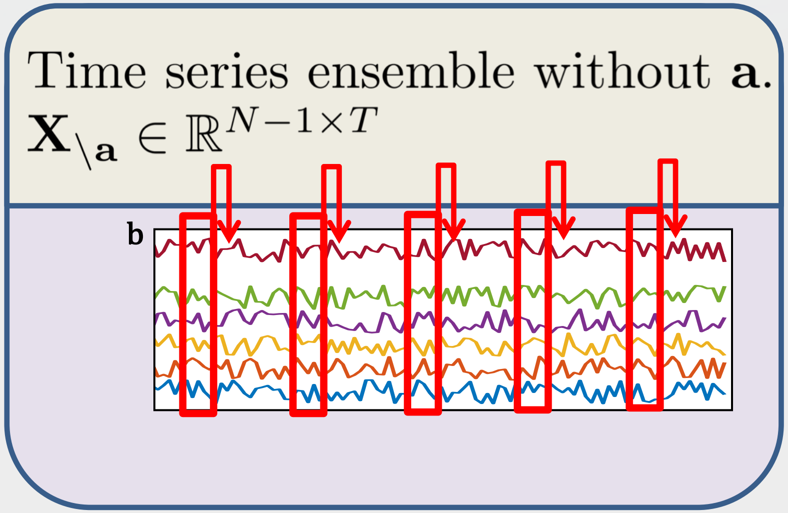
We get an estimate $\widehat{\mathbf{X}}$ using VAR modelling. $\mathbf{AR}_j \in \mathbb{R}^{N\times N}$ are the model parameters. m is the order of the process.

Granger Causality*

If the prediction quality of **b** improves when the past of **a** is used in its prediction as compared to its quality of prediction in the absence of **a**, then **a** *Granger Causes* **b**



Full ensemble of time series, $\mathbf{X} \in \mathbb{R}^{N \times T}$



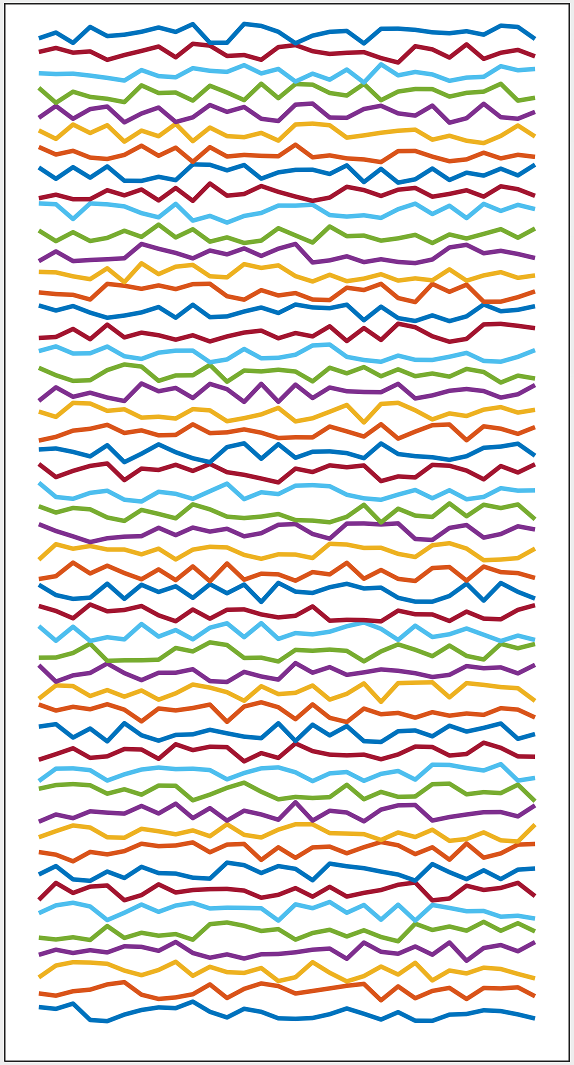
Time series ensemble without $\mathbf{a}$. $\mathbf{X}_{\setminus\mathbf{a}} \in \mathbb{R}^{N-1 \times T}$

$$F_{\mathbf{a}\to\mathbf{b}} = \log \frac{\sigma(e_{\mathbf{b}\mathbf{X}_{\setminus\mathbf{a}}})}{\sigma(e_{\mathbf{b}\mathbf{X}})} \quad \text{where, } e_{\mathbf{b}\mathbf{X}_{\setminus\mathbf{a}}} = \mathbf{b} - \hat{\mathbf{b}}_{\mathbf{X}_{\setminus\mathbf{a}}}$$

*Seth, A. K., Barrett, A. B., & Barnett, L. (2015). Granger causality analysis in neuroscience and neuroimaging. *Journal of Neuroscience*, *35*(8), 3293-3297

Limitation(s)

- Cannot be extended to a full brain analysis as $N \gg T$
    - As N increases number of parameter increase by N^2
    - This results in an under-determined problem.
- Granger causality is generally applied on fMRI datasets through
    - a priori ROI selection
    - Longer time series



Large scale Granger Causality (lsGC)*

- We try to circumvent the $N \gg T$ problem
- Incorporate an additional step of invertible dimension reduction
- We can obtain the ***directional information*** scores at ***voxel*** level, in a ***multivariate*** sense

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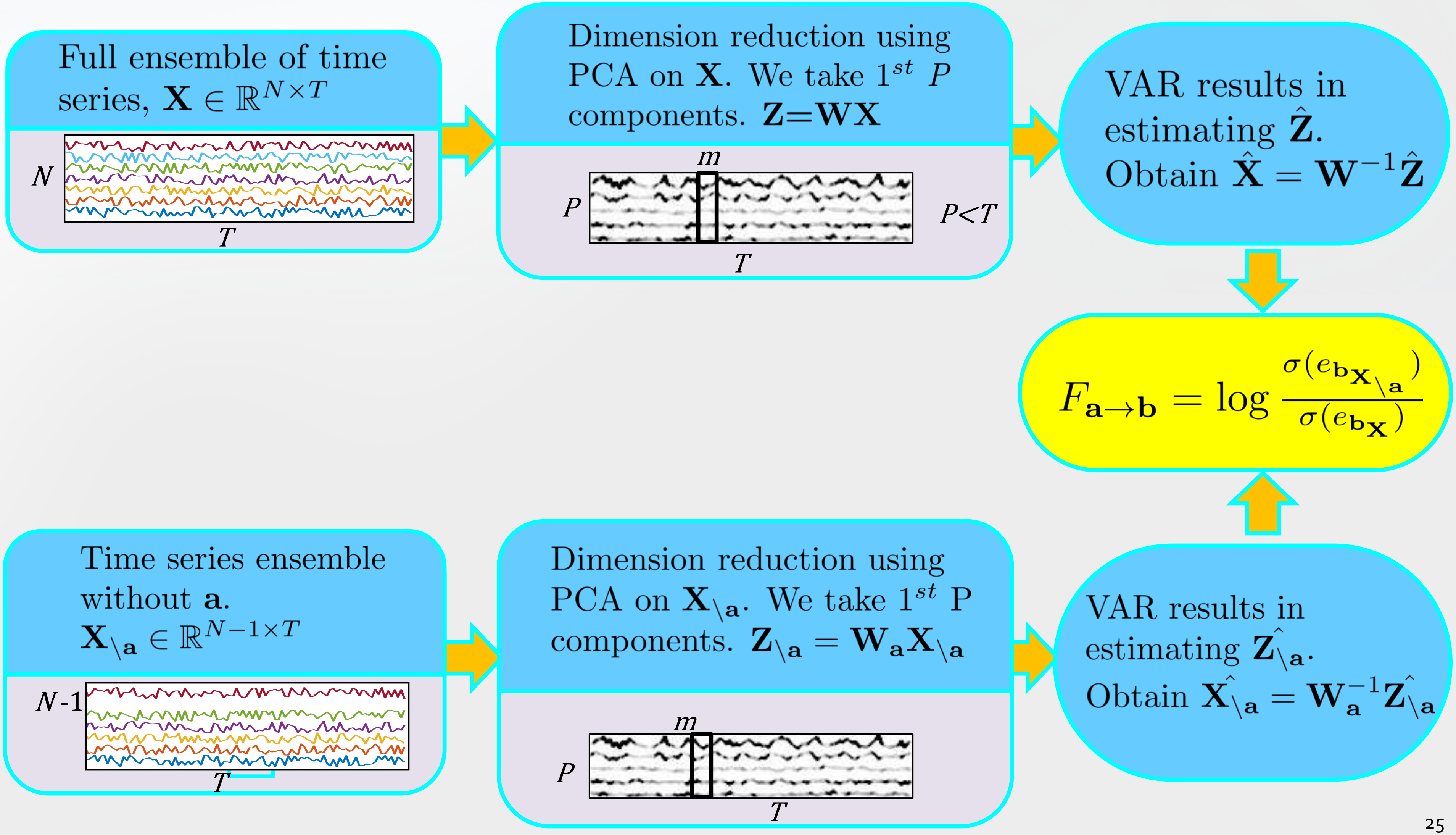
* DSouza, A. M., Abidin, A. Z., et. al. (2017). Exploring Connectivity with Large-Scale Granger Causality on Resting-State Functional MRI. *Journal of Neuroscience Methods*.

Large scale Granger Causality (lsGC)



Full ensemble of time series, $\mathbf{X} \in \mathbb{R}^{N \times T}$

Dimension reduction using PCA on $\mathbf{X}$. We take 1^{st} P components. $\mathbf{Z}$=$\mathbf{WX}$

VAR results in estimating $\hat{\mathbf{Z}}$. Obtain $\hat{\mathbf{X}} = \mathbf{W}^{-1}\hat{\mathbf{Z}}$

$$F_{\mathbf{a}\rightarrow\mathbf{b}} = \log \frac{\sigma(e_{\mathbf{b}\mathbf{X}_{\setminus\mathbf{a}}})}{\sigma(e_{\mathbf{b}\mathbf{X}})}$$

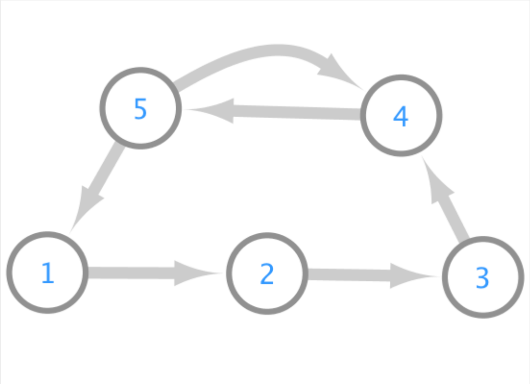
Time series ensemble without **a**. $\mathbf{X}_{\setminus\mathbf{a}} \in \mathbb{R}^{N-1 \times T}$

Dimension reduction using PCA on $\mathbf{X}_{\setminus\mathbf{a}}$. We take 1^{st} P components. $\mathbf{Z}_{\setminus\mathbf{a}} = \mathbf{W}_{\mathbf{a}}\mathbf{X}_{\setminus\mathbf{a}}$

VAR results in estimating $\hat{\mathbf{Z}}_{\setminus\mathbf{a}}$. Obtain $\hat{\mathbf{X}}_{\setminus\mathbf{a}} = \mathbf{W}_{\mathbf{a}}^{-1}\hat{\mathbf{Z}}_{\setminus\mathbf{a}}$

Large scale Granger Causality (lsGC)

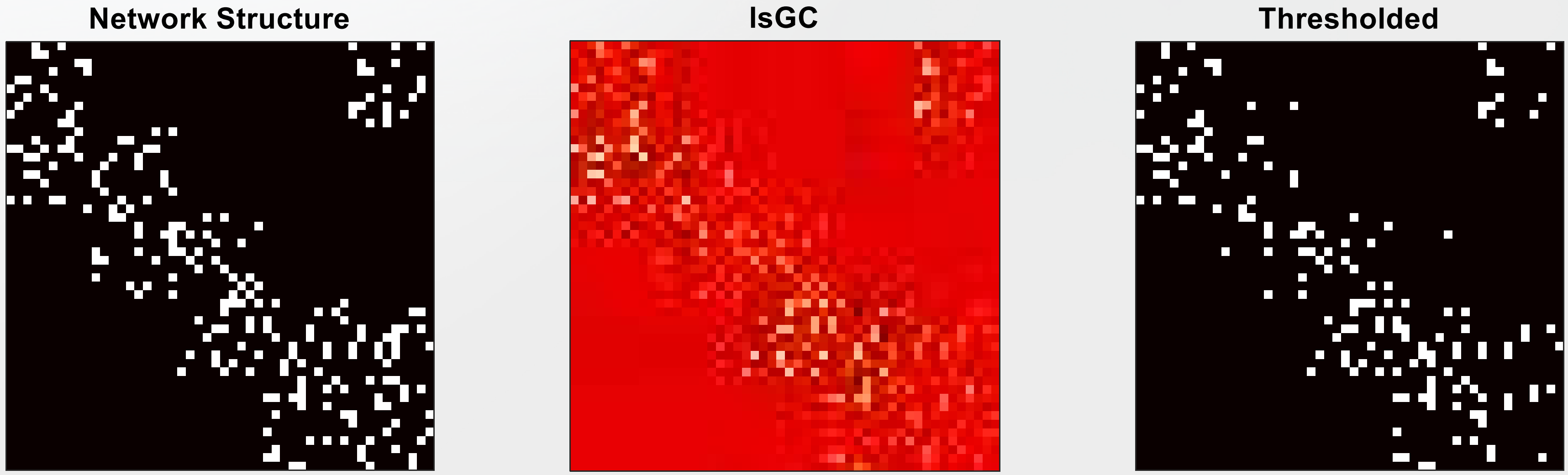
- To validate this lsGC we generated a system of time-series with known structure
- 50-dimensional stationary multivariate autoregressive (MVAR) processes of order two were generated



- Corresponding AR parameters were chosen according to Baccala et. al.
- Network consists of 5 clusters

Baccalá, Luiz A., and Koichi Sameshima. "Partial directed coherence: a new concept in neural structure determination." *Biological cybernetics*84.6 (2001): 463-474.

Large scale Granger Causality (lsGC)



AUC = 0.91

csen = 0.87

Validation(s) – fMRI simulations

- Realistic fMRI simulations
  - As proposed by Smith et. al.* specifically for validation of network modelling methods
  - Based on the dynamic causal modelling with non-linear hemodynamic response on top of a neural network

- Network of varied complexity can be used for simulation of BOLD time-series

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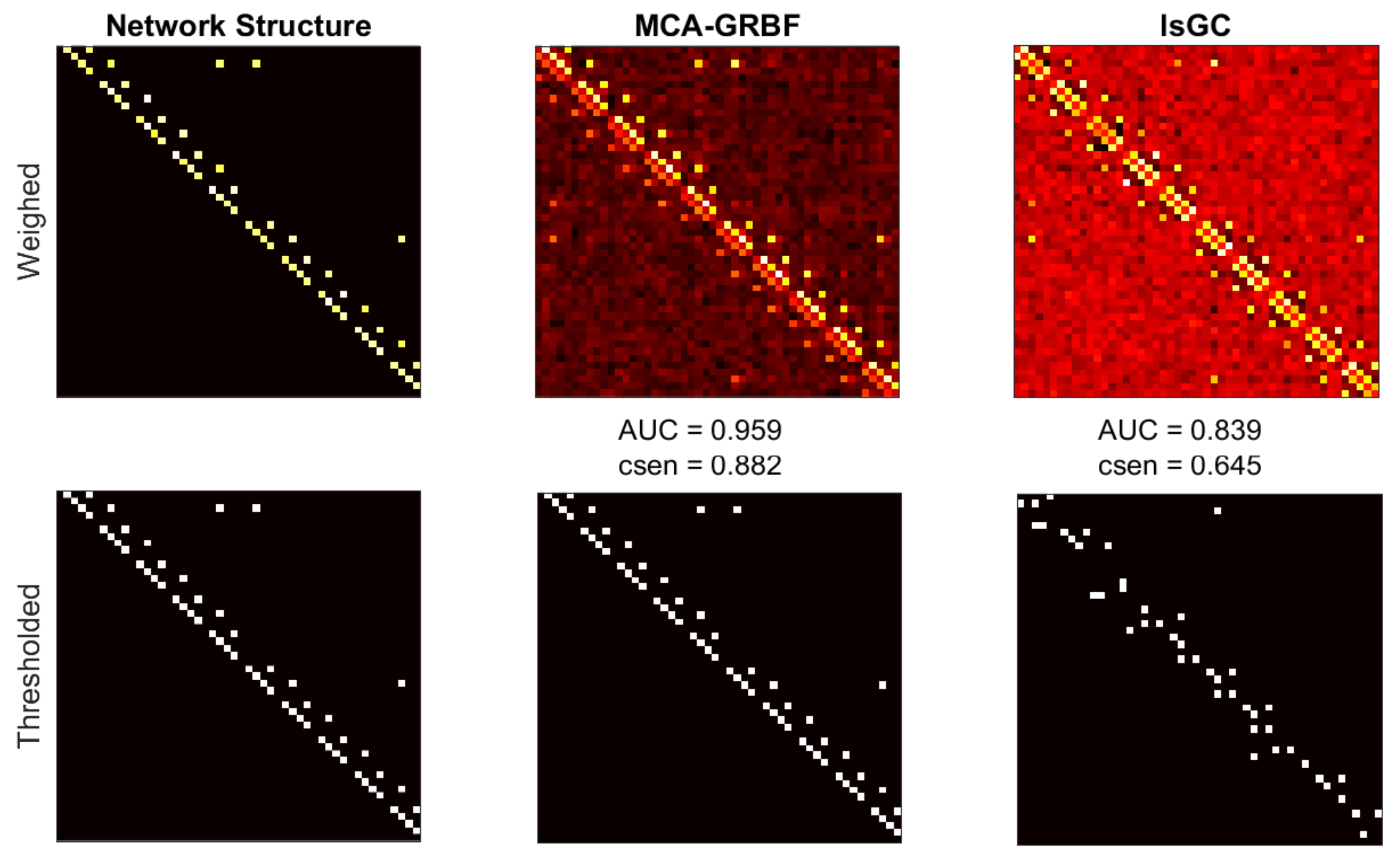
* Smith, Stephen M., et al. "Network modelling methods for FMRI." *Neuroimage* 54.2 (2011): 875-891.

Validation(s) – fMRI simulations

Results over 50 iterations for each simulation



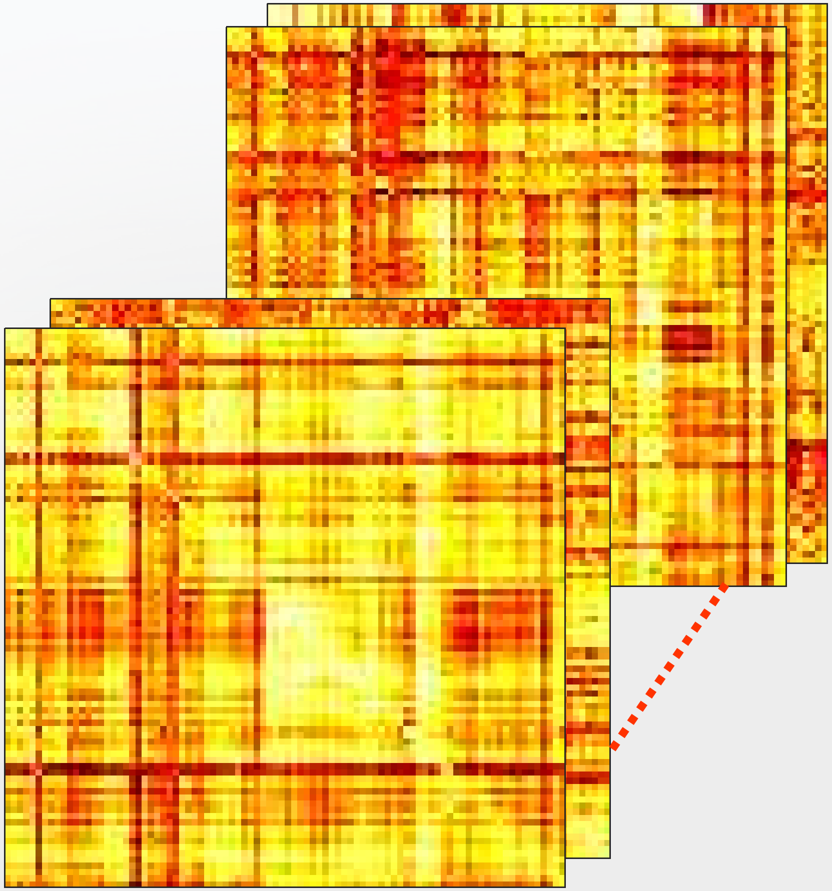
Comparative Analysis

- Conventional Methods
  - Correlation based analysis (*linear, bivariate*)
  - Mutual information (*non-linear, bivariate*)
  - Partial correlation (*linear, multi-variate*)

Specific Aims

2. **To model a suitable network analysis framework for identifying changes in the brain connectivity profiles.**
   - Quantitatively characterize the network profiles (at a global as well as regional level) based on graph theoretic approaches with the aim of developing imaging-derived biomarkers for disease.
   - Apply and adapt the network based statistic framework for analyzing connectivity profiles to detect edge level effects of disease.
   - Develop a statistical framework for performing seed-based connectivity in a non-linear and multivariate sense for studying whole-brain connectivity maps.

Approach



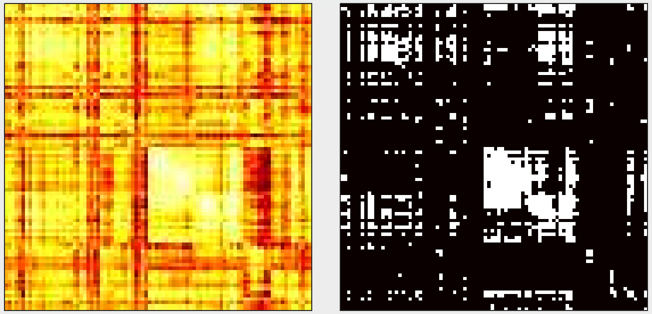
- The connectivity matrices obtained in Aim 1 can be considered as representative network graphs
- A graph consists of *nodes* and *edges* (pair-wise interactions)

- A system with N nodes results in a graph with $N(N-1)$ edges.

Approach – Graph Theoretic Measures

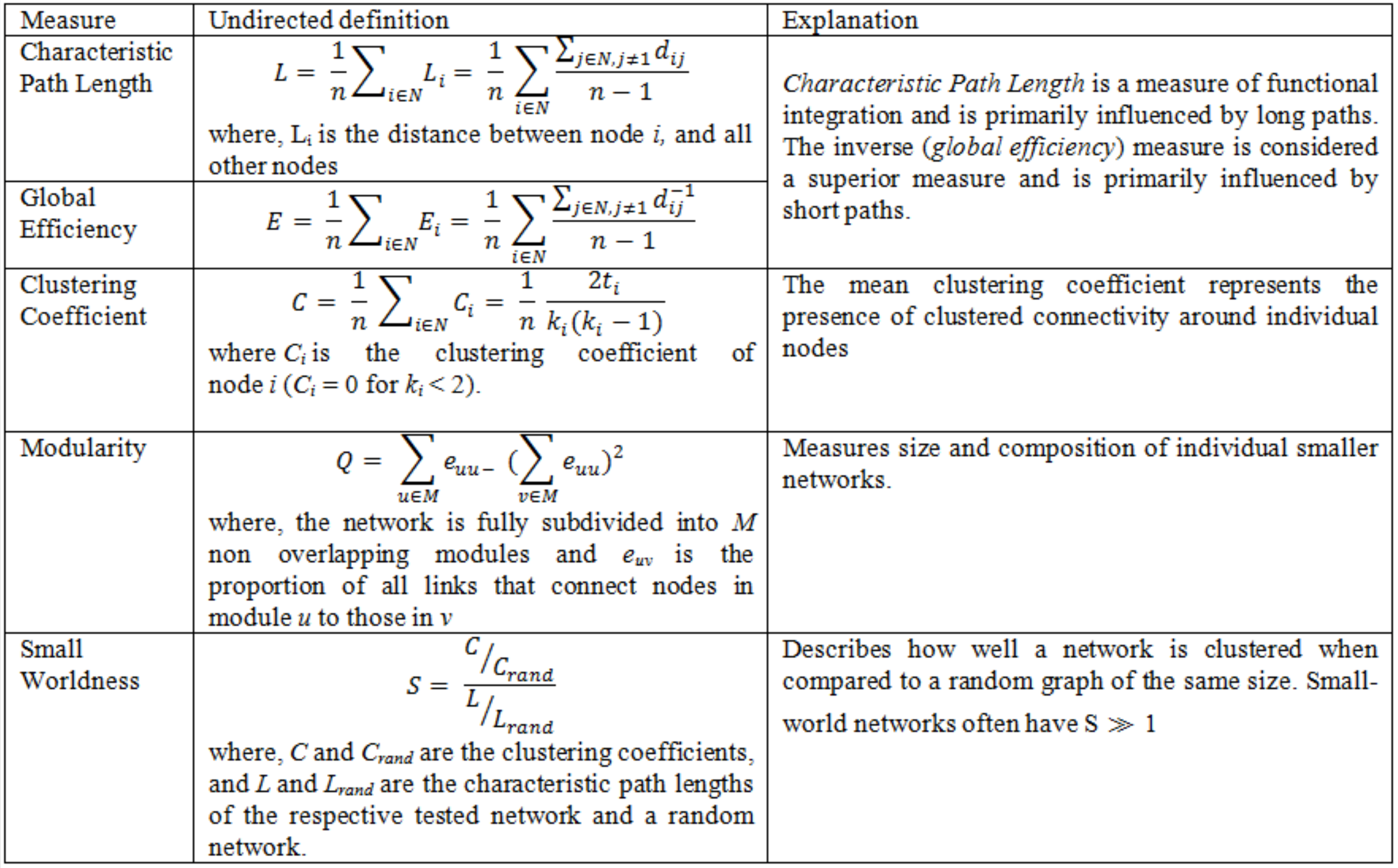
- Can characterize local or global properties
- Can be specific to nodes or the actual links
- If these are based on nodes then they are characterized by a distribution (based on the number of nodes).

1. Functional Segregation
2. Functional Integration
3. Small World Properties
4. Network Motifs &Centrality
5. Resilience



- **Degree** : Number of nodes connected to an individual node
- **Distribution** : Degrees of all nodes comprise this. Mean is measure of density or the total wiring cost of the network.

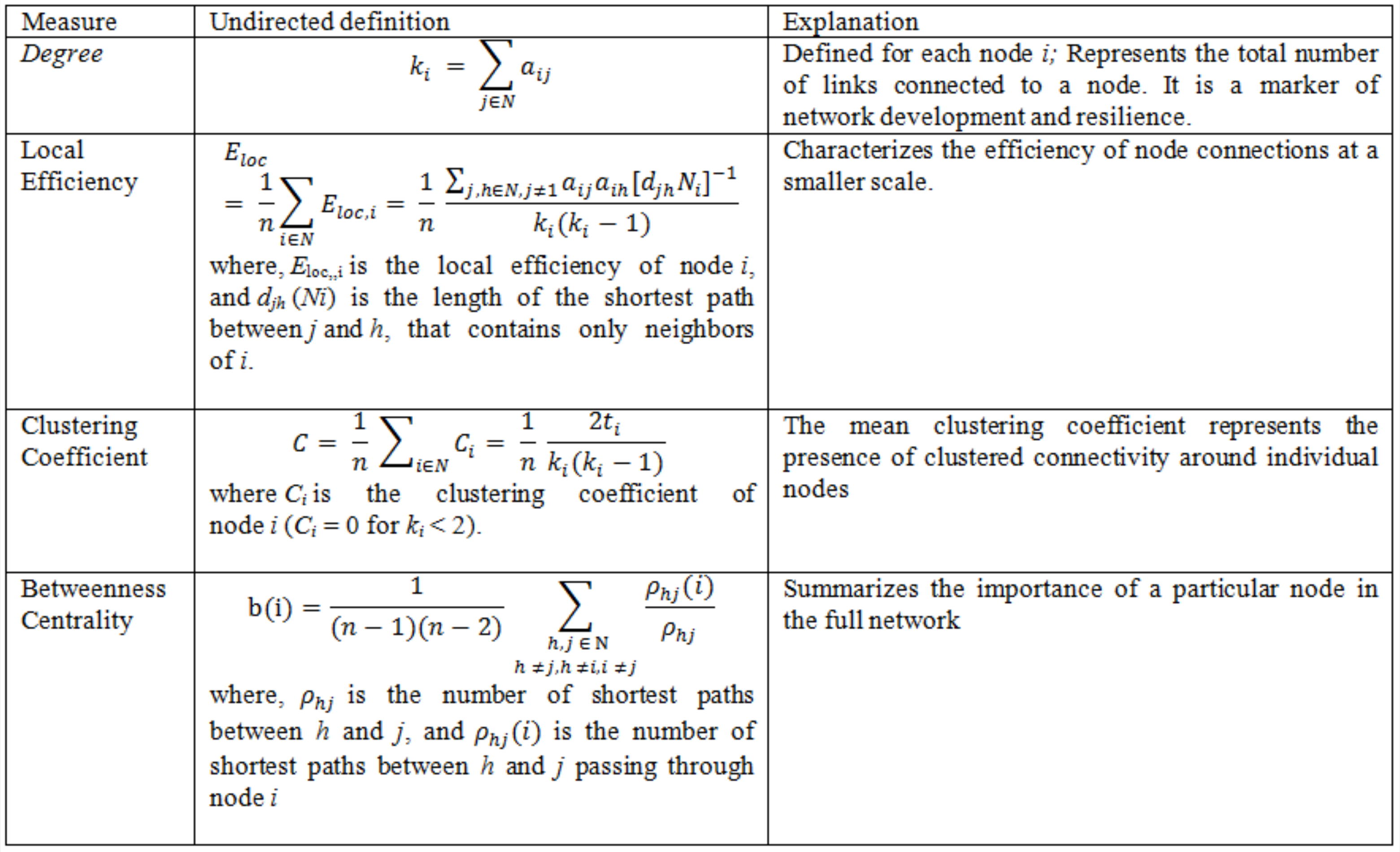
Global Graph Measures



Measure	Undirected definition	Explanation
Characteristic Path Length	$L = \frac{1}{n}\sum_{i\in N} L_i = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq 1} d_{ij}}{n-1}$ where, L_i is the distance between node *i*, and all other nodes	*Characteristic Path Length* is a measure of functional integration and is primarily influenced by long paths. The inverse (*global efficiency*) measure is considered a superior measure and is primarily influenced by short paths.
Global Efficiency	$E = \frac{1}{n}\sum_{i\in N} E_i = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq 1} d_{ij}^{-1}}{n-1}$	
Clustering Coefficient	$C = \frac{1}{n}\sum_{i\in N} C_i = \frac{1}{n}\frac{2t_i}{k_i(k_i-1)}$ where C_i is the clustering coefficient of node *i* ($C_i = 0$ for $k_i < 2$).	The mean clustering coefficient represents the presence of clustered connectivity around individual nodes
Modularity	$Q = \sum_{u\in M} e_{uu} - (\sum_{v\in M} e_{uu})^2$ where, the network is fully subdivided into M non overlapping modules and e_{uv} is the proportion of all links that connect nodes in module u to those in v	Measures size and composition of individual smaller networks.
Small Worldness	$S = \frac{C/C_{rand}}{L/L_{rand}}$ where, C and C_{rand} are the clustering coefficients, and L and L_{rand} are the characteristic path lengths of the respective tested network and a random network.	Describes how well a network is clustered when compared to a random graph of the same size. Small-world networks often have $S \gg 1$

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*, *52*(3), 1059-1069.

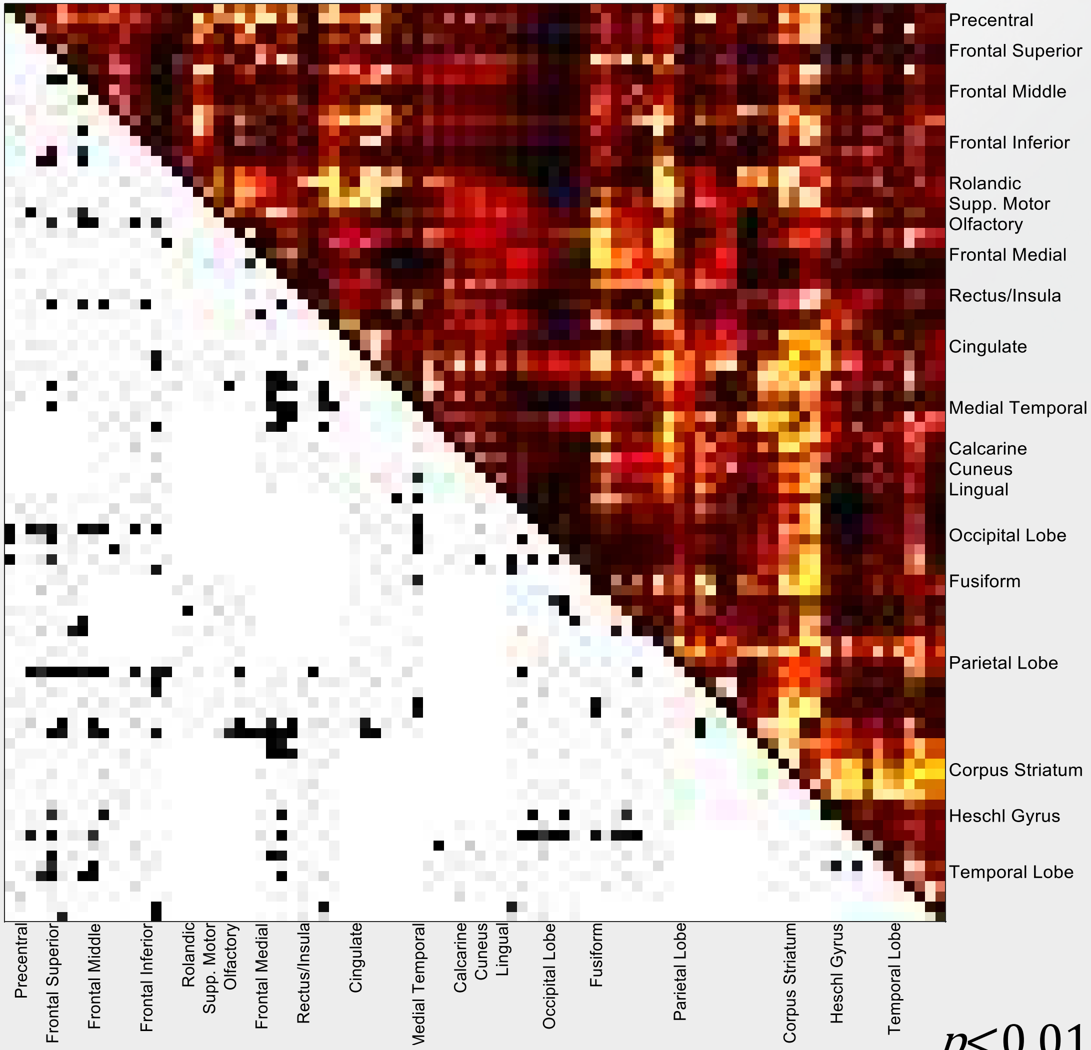
Regional Characteristics

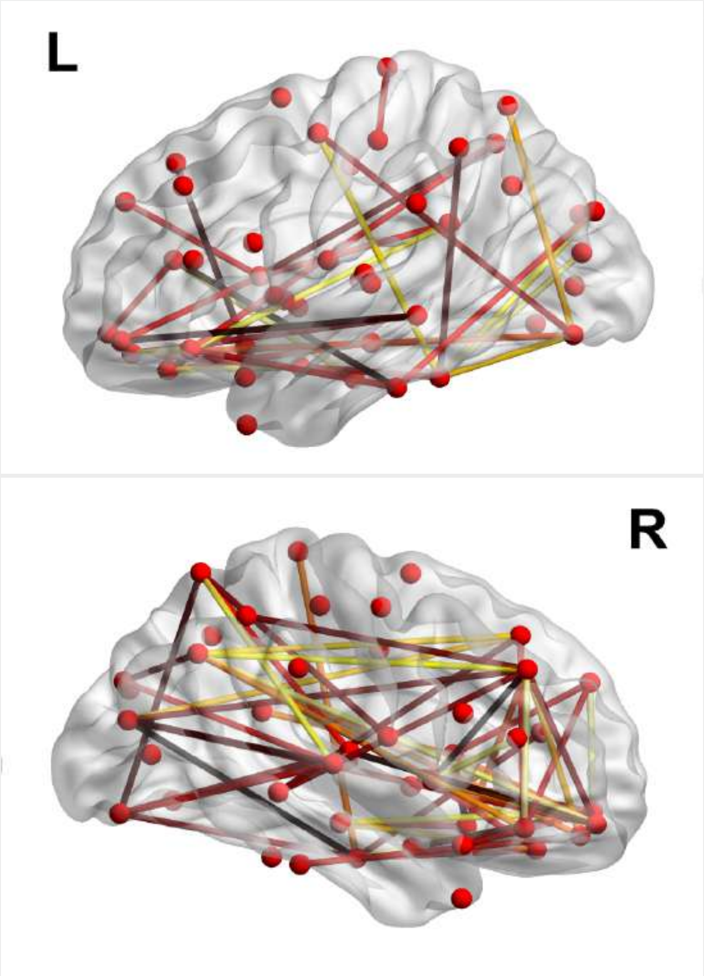


Measure	Undirected definition	Explanation
Degree	$k_i = \sum_{j\in N} a_{ij}$	Defined for each node *i;* Represents the total number of links connected to a node. It is a marker of network development and resilience.
Local Efficiency	$E_{loc} = \frac{1}{n}\sum_{i\in N} E_{loc,i} = \frac{1}{n}\frac{\sum_{j,h\in N, j\neq 1} a_{ij}a_{ih}[d_{jh}N_i]^{-1}}{k_i(k_i-1)}$ where, $E_{loc,,i}$ is the local efficiency of node *i*, and d_{jh} (*Ni*) is the length of the shortest path between *j* and *h*, that contains only neighbors of *i*.	Characterizes the efficiency of node connections at a smaller scale.
Clustering Coefficient	$C = \frac{1}{n}\sum_{i\in N} C_i = \frac{1}{n}\frac{2t_i}{k_i(k_i-1)}$ where C_i is the clustering coefficient of node *i* ($C_i = 0$ for $k_i < 2$).	The mean clustering coefficient represents the presence of clustered connectivity around individual nodes
Betweenness Centrality	$b(i) = \frac{1}{(n-1)(n-2)} \sum_{\substack{h,j\in N \\ h\neq j, h\neq i, i\neq j}} \frac{\rho_{hj}(i)}{\rho_{hj}}$ where, ρ_{hj} is the number of shortest paths between *h* and *j*, and $\rho_{hj}(i)$ is the number of shortest paths between *h* and *j* passing through node *i*	Summarizes the importance of a particular node in the full network

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*, *52*(3), 1059-1069.

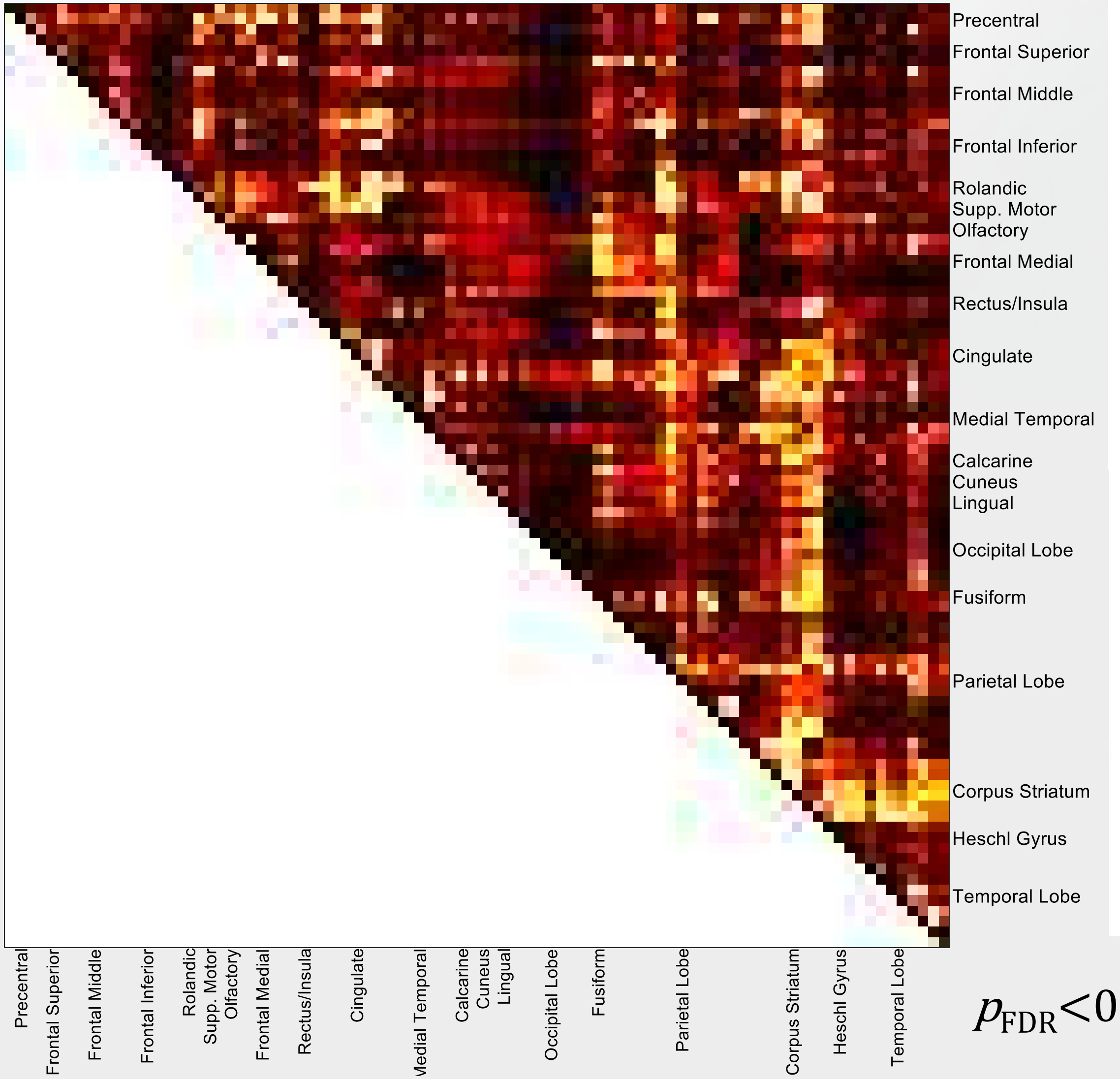
Edge-specific differences

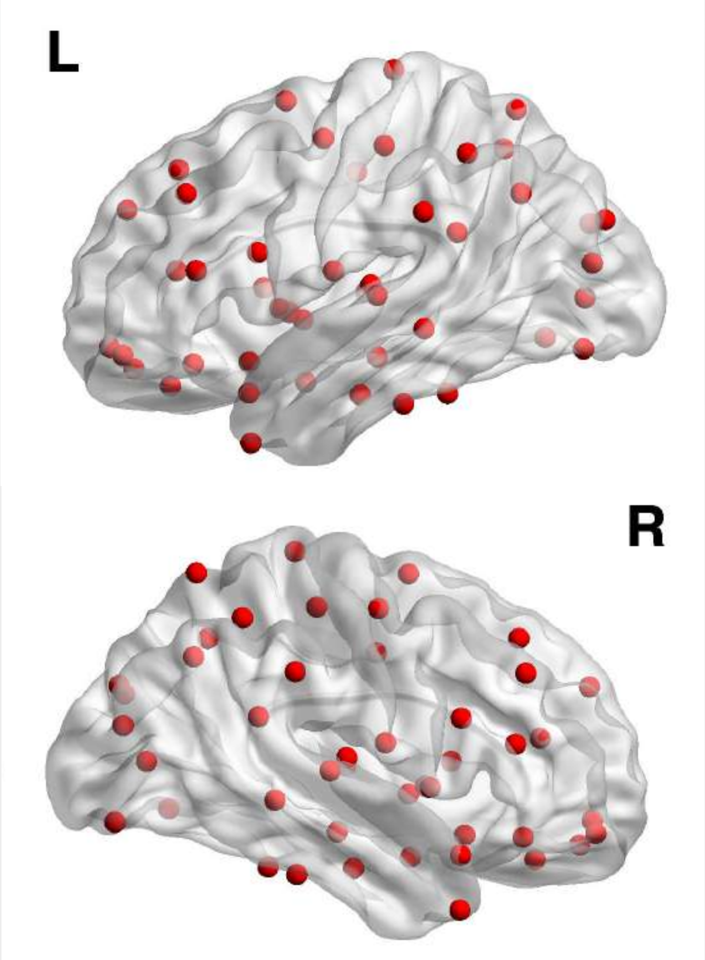




$p<0.01$

Edge-specific differences





$p_{\mathrm{FDR}} < 0.05$

Network-Based Statistic*

- The NBS approach offers better control over Family wise error when multiple comparisons are required.
- It seeks to identify connected nodes or clusters instead of focusing only on individual links.

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* Zalesky, A., Fornito, A., & Bullmore, E. T. "Network-based statistic: identifying differences in brain networks." *Neuroimage* 53, no. 4 1197-1207. (2010):

Network-Based Statistic*

- A t-statistic is computed for each link to define a set of links above a threshold of ($p=0.05$).
- A non-parametric permutation approach (5000 permutations) is used to estimate the significance of the individual components (each of size M_i).
- The null distribution of the maximal component size for each iteration is obtained
- The corrected p-value is determined by calculating the proportion of the 5000 permutations for which the maximal connected component was larger than M_i.

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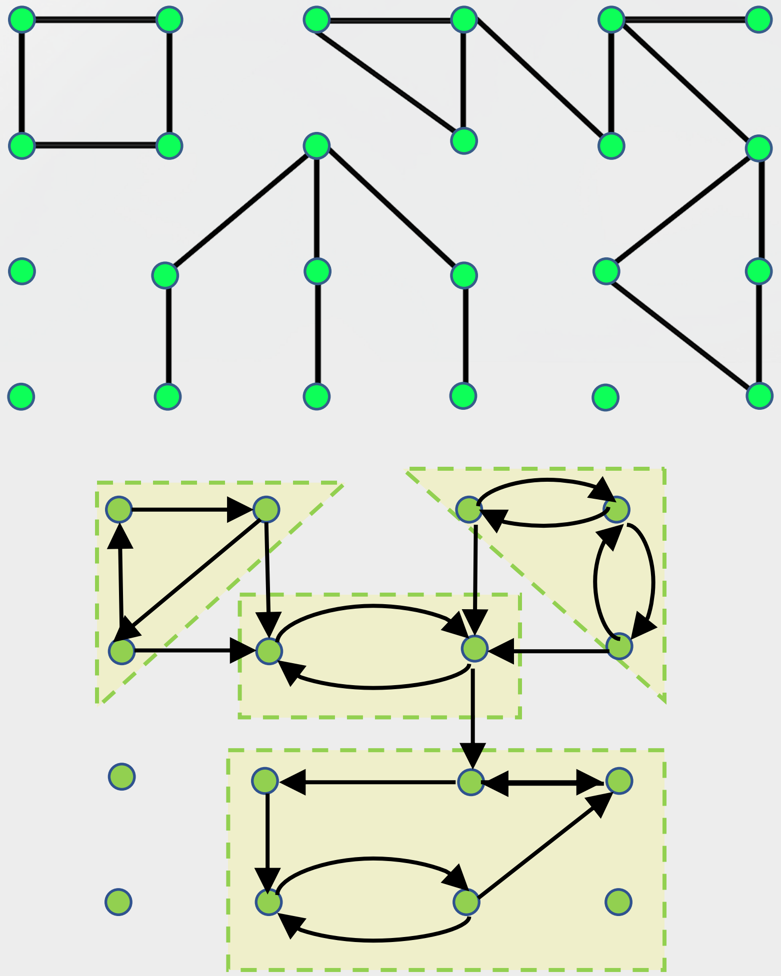
* Zalesky, A., Fornito, A., & Bullmore, E. T. "Network-based statistic: identifying differences in brain networks." *Neuroimage* 53, no. 4 1197-1207. (2010):

Network-Based Statistic

- The critical step here is the detection of connected components
- In the case of undirected networks, it is done via a simple breadth first search
- For directed networks, ‘strongly’ connected components can be obtained using Kosaraju’s algorithm



Seed Based Connectivity

- Define a seed or a region of interest in the brain
- Compute connectivity with all other voxels

- Gives an option of quantifying the extent of connections
- A more interpretable notion of connectivity

- With methods developed in Aim 1 we can also detect the notion of directed connectivity

Seed Based Connectivity – MCA-GRBF

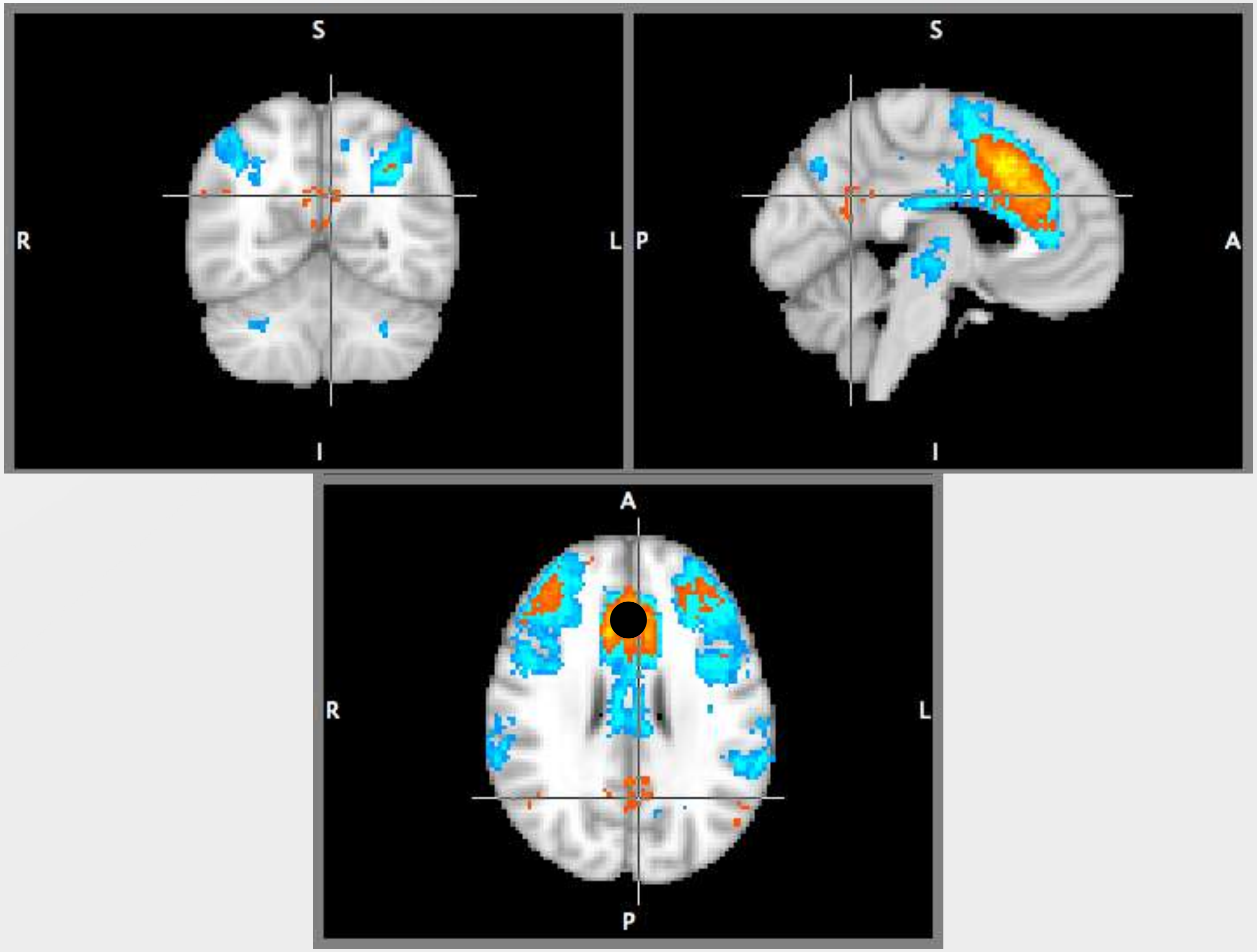
Preliminary Result

Seed –
Anterior Cingulate
Gyrus

Blue/Light Blue –
Correlation Map

Red/Yellow –
MCA-GRBF

Simple Mean Effect
p<0.05, FDR
corrected



Seed Based Connectivity – MCA-GRBF

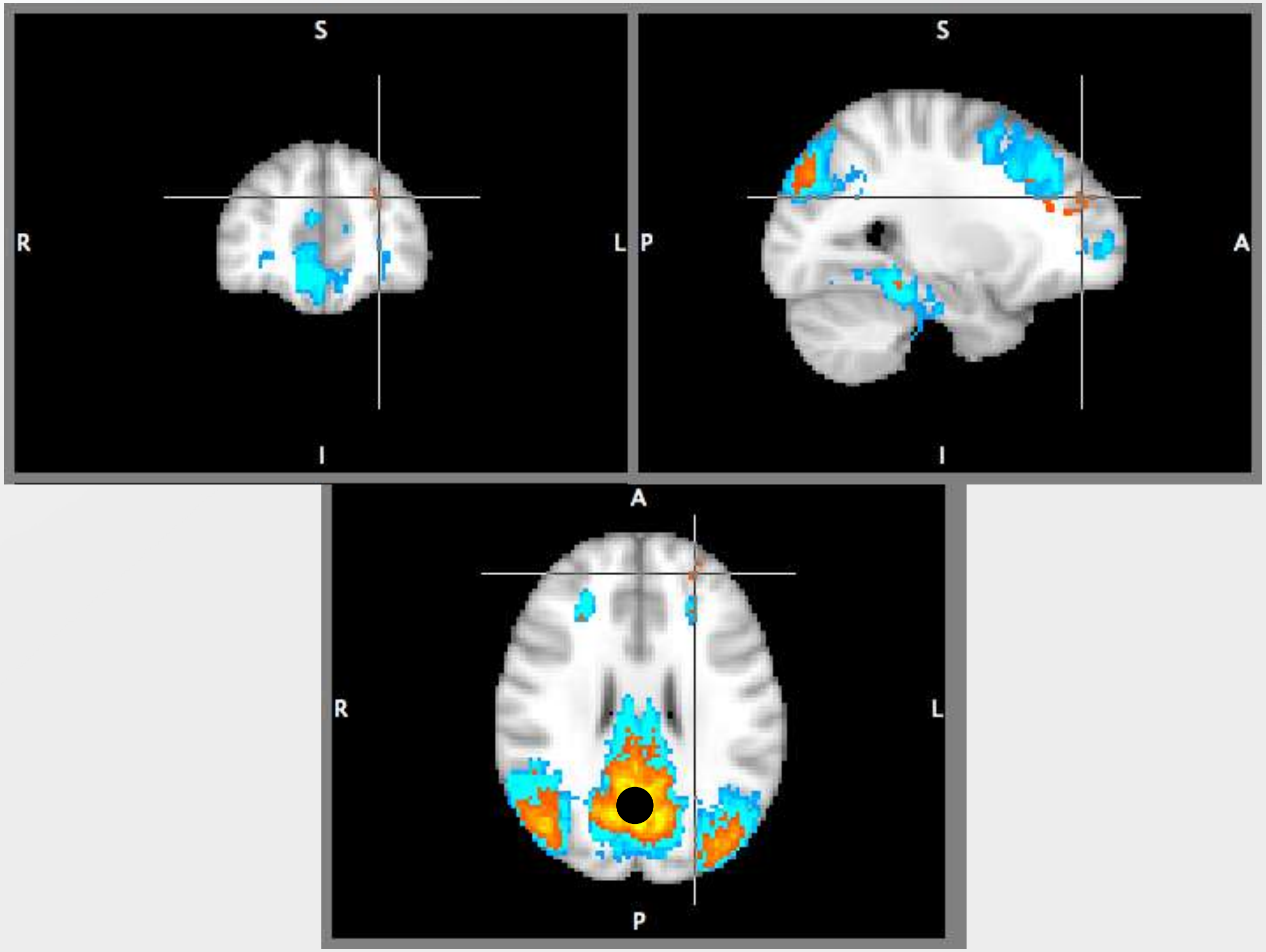
Preliminary Result

Seed –
Posterior Cingulate
Gyrus

Blue/Light Blue –
Correlation Map

Red/Yellow –
MCA-GRBF

Simple Mean Effect
p<0.05, FDR
corrected



Seed Based Connectivity

- Conventionally, most studies are based on a correlation analysis
  - Bivariate in nature
- Directional information (seed-to-voxel as well as voxel to seed) effects can be studied
- Multivariate techniques for such an analysis are less explored
- The lsGC framework can enable a purely multivariate seed based analysis, not performed previously

Specific Aims

3. **To quantitatively evaluate our system in a clinical pilot study by performing an in-depth assessment of changes in resting-state brain activity in subjects with HIV infection.**
   - Preprocess and analyze clinical, neuropsychological testing and neuroimaging data acquired in a pilot study for identifying subjects with HAND based on current clinical standards.
   - Evaluate relationships between neuropsychological testing scores and connectivity derived summary measures, for assessing their applicability as clinical biomarkers.
   - Assess regional changes in brain networks occurring as a result of neural injury caused by HIV infection.

HIV Associated Neurocognitive Disorder (HAND)

- Synpato-dendritic complex has been shown to loose its densely branched structure during HIV infection
- Can occur long before symptoms manifest in an individual
- Such damage can trigger changes in global connectivity

- The efficacy of treatment paradigm (particularly cART – combined anti-retroviral therapy) has helped dramatically control viral loads HIV+ individuals leading to longer life expectancy

HIV Associated Neurocognitive Disorder (HAND)

- Before cART severe dementia could affect ~20% of the individuals
- Following cART, the incidence of severe disabling dementia has reduced however milder forms of the disorder are prevalent
- Neuropsychologic performance testing is the clinical standard for both diagnosis and monitoring
  - It can miss subtle effects of disease

Approach – Data

- 40 subjects were recruited at the University of Rochester Medical Center, as part of a NIH funded study (R01-DA-034977).
- Imaging Protocol:
  - MPRAGE scan (TI = 950 ms, TE/TR = 3.87 ms/1,620 ms, 1-mm isotropic resolution)
  - 4 gradient echo (GE) EPI sequences, with the following parameters: 25 contiguous axial slices, 4mm slice thickness, TR=1650 ms, TE= 23ms, 96x96 matrix – 240 time points
- Detailed neuropsychological testing
  - executive function, information processing speed, attention and working memory, learning, memory, motor function etc.

Demographics & Clinical characteristics

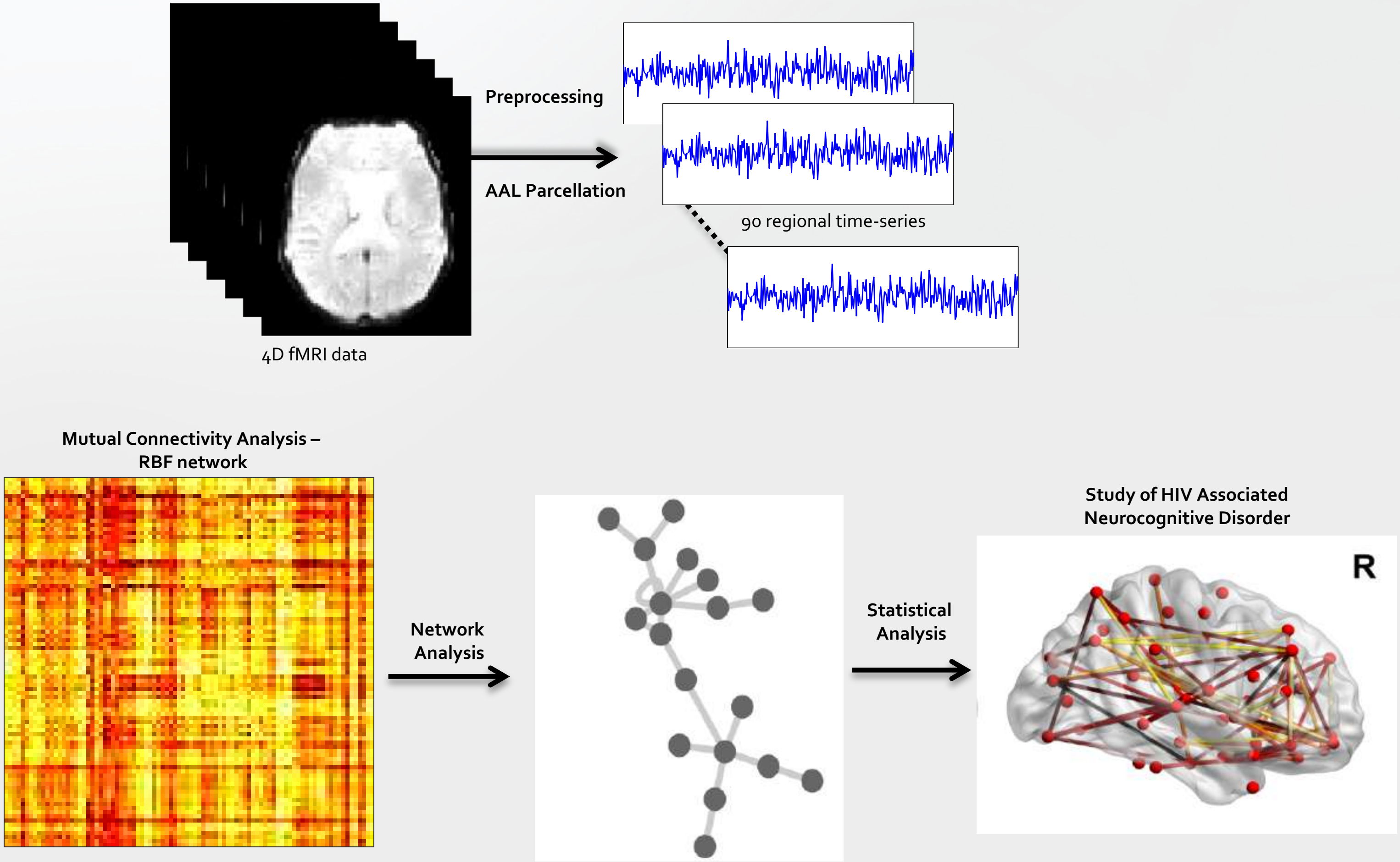
	HIV-		HIV+	
Number of Patients	20		20	
Age – in years	41.45	(9.98)	41.60	(15.42)
Gender (Num. female/male)	9/11		5/15	
Nadir CD4 (cells/mm^3)	-NA-		314.63	(211.94)
CD4 (cells/mm^3)	-NA-		702.8	(464.5)
VL (log$_{10}$ scale)	-NA-		1.76	(1.79)
HIV - in years	-NA-		11.44	(9.11)
<u>NP Z-scores</u>				
Attention	0.432	(0.8)	-0.541	(1.042)
Executive	0.284	(0.982)	-0.36	(0.953)
Learning	0.363	(0.915)	-0.323	(0.878)
Memory	0.345	(1.04)	-0.254	(0.76)
Motor	0.536	(0.664)	-0.54	(0.957)
Speed of Information Processing	0.366	(0.769)	-0.42	(1.066)
Overall	2.327	(2.842)	-2.41	(3.711)
<u>HAND Classification (%)</u>				
WNL	-NA-		6	(30%)
ANI	-NA-		12	(60%)
MND	-NA-		2	(10%)

Approach – Data

- Standard preprocessing
  - Motion correction
  - Linear detrending
  - Correction for interleaved acquisition
  - Normalization the MNI template

- Anatomic Parcellation
  - AAL template (90 regions)
  - Dosenbach template (160 regions)

Approach



Preprocessing

AAL Parcellation

4D fMRI data

90 regional time-series

Mutual Connectivity Analysis – RBF network

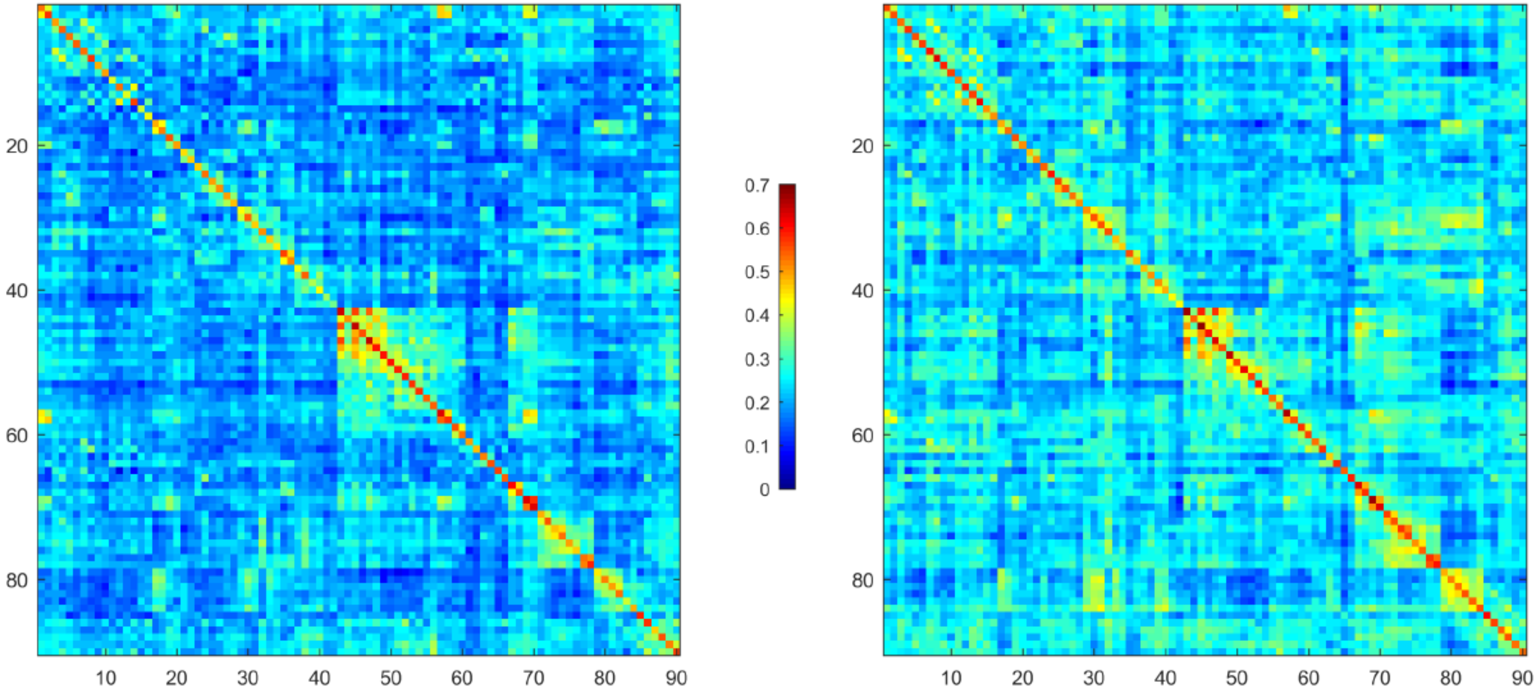
Network Analysis

Statistical Analysis

Study of HIV Associated Neurocognitive Disorder

Non-Linear Connectivity

- Mean Group Matrices – MCA GRBF



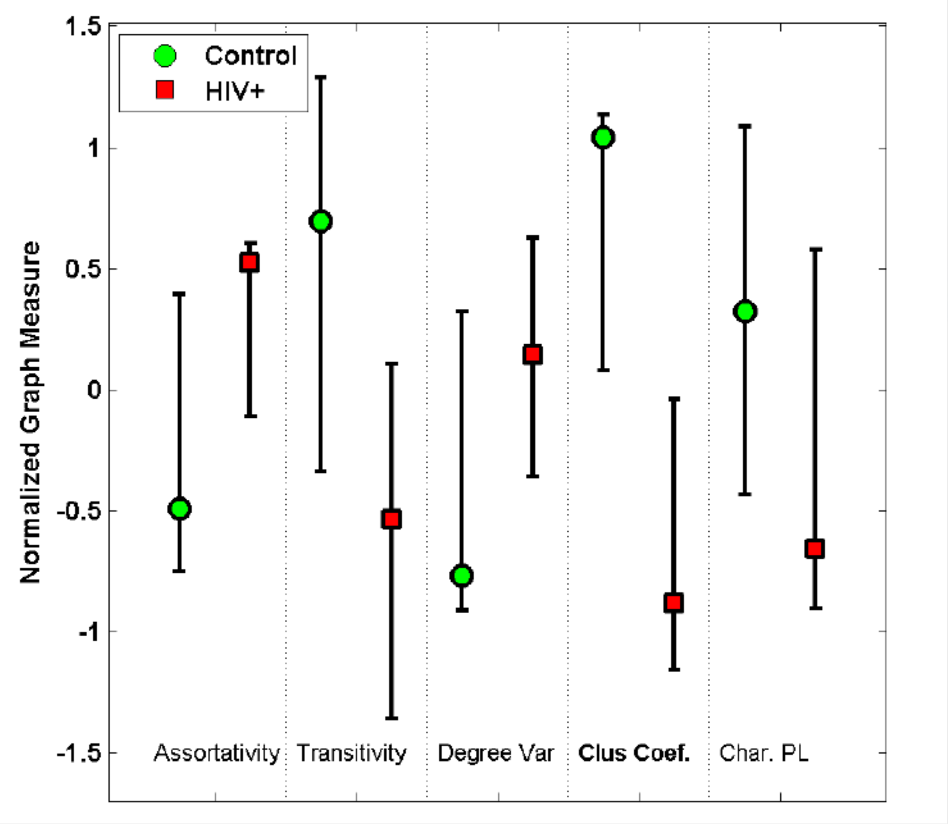
HIV -

HIV +

Global Graph Statistics

- Comparison between subjects with and without HIV infection

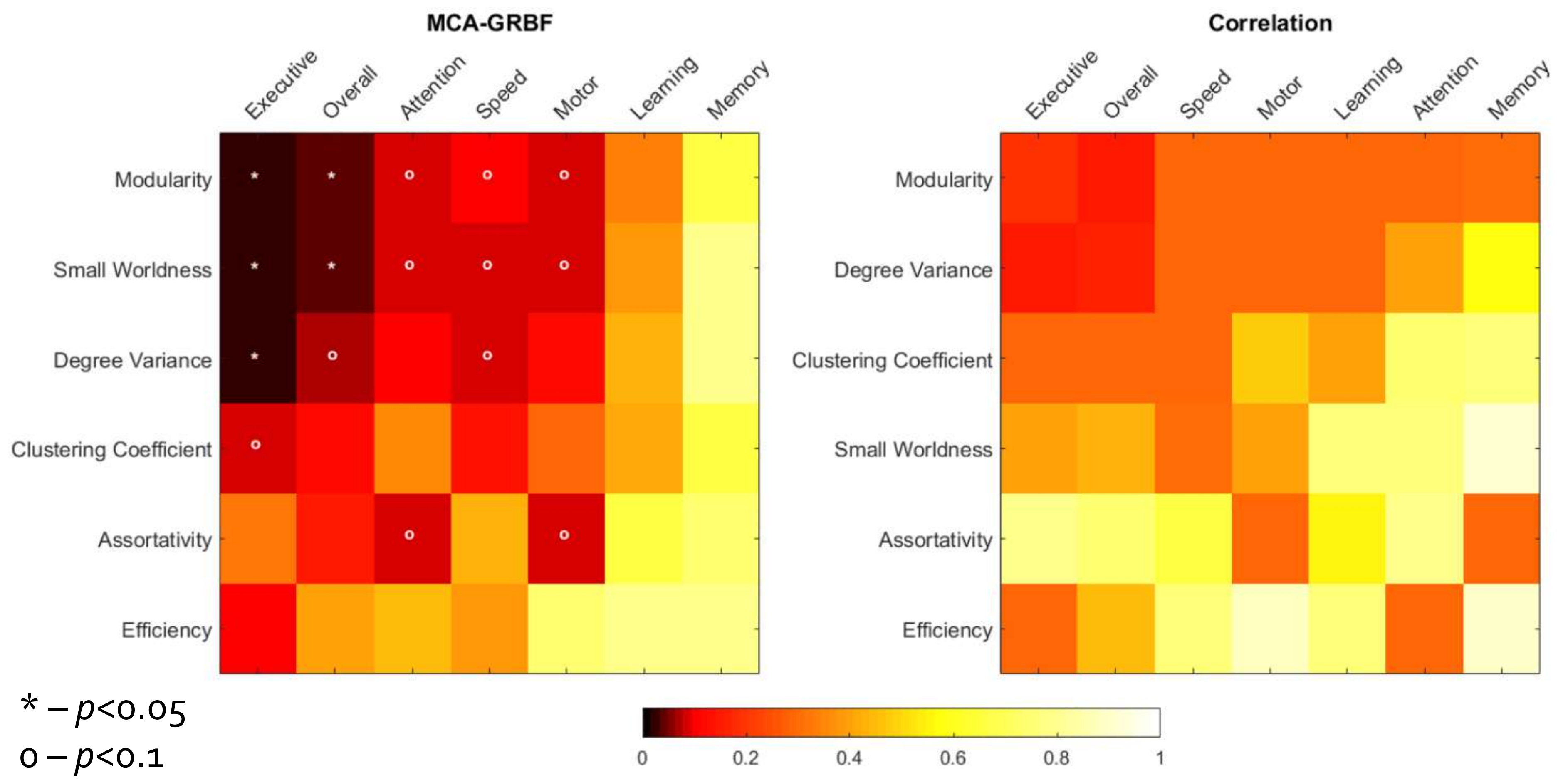
- Regression analysis when controlled for age and gender



Abidin et. al. "Investigating changes in brain network properties in HIV-associated neurocognitive disease (HAND) using mutual connectivity analysis (MCA)." In SPIE Medical Imaging, pp. 97881W-97881W. 2016.

Global Graph Statistics

- Associations with NP assessment scores



* – $p<0.05$

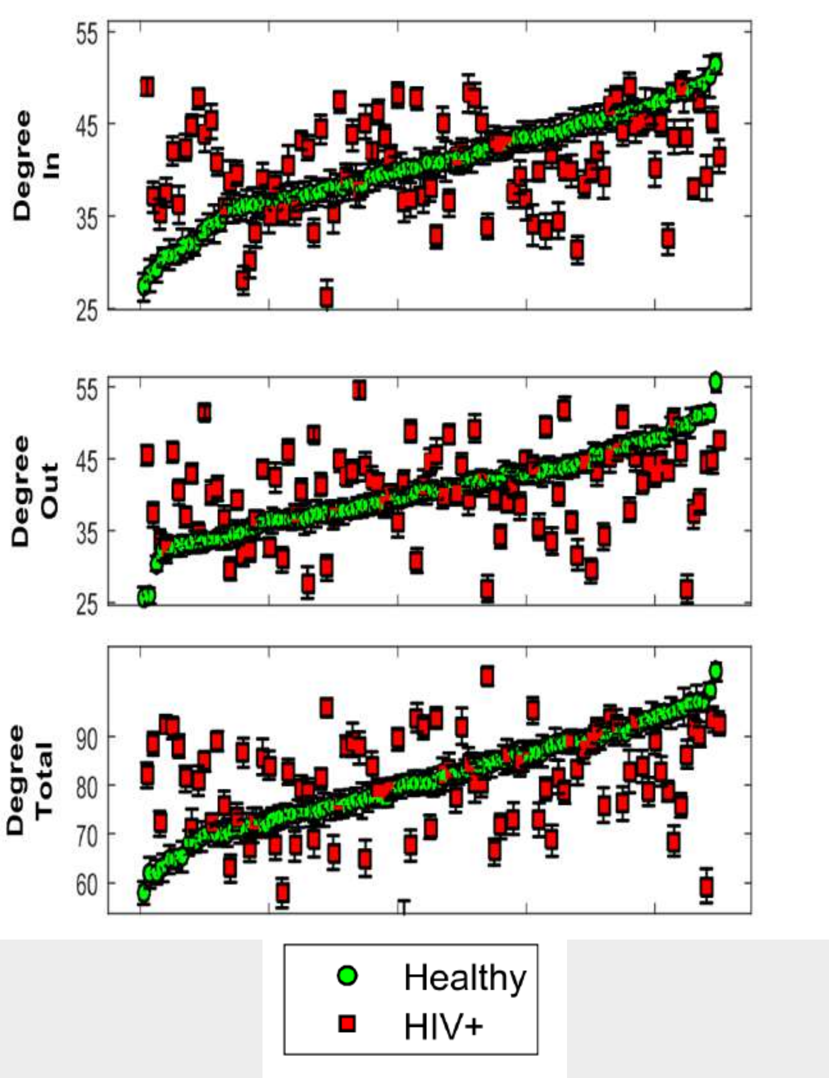
o – $p<0.1$

Abidin et. al. "Alteration of Brain Network Topology in HIV Associated Neurocognitive Disorder: A Novel Functional Connectivity Perspective". Neuroimage Clinical (2017), *Under Review*

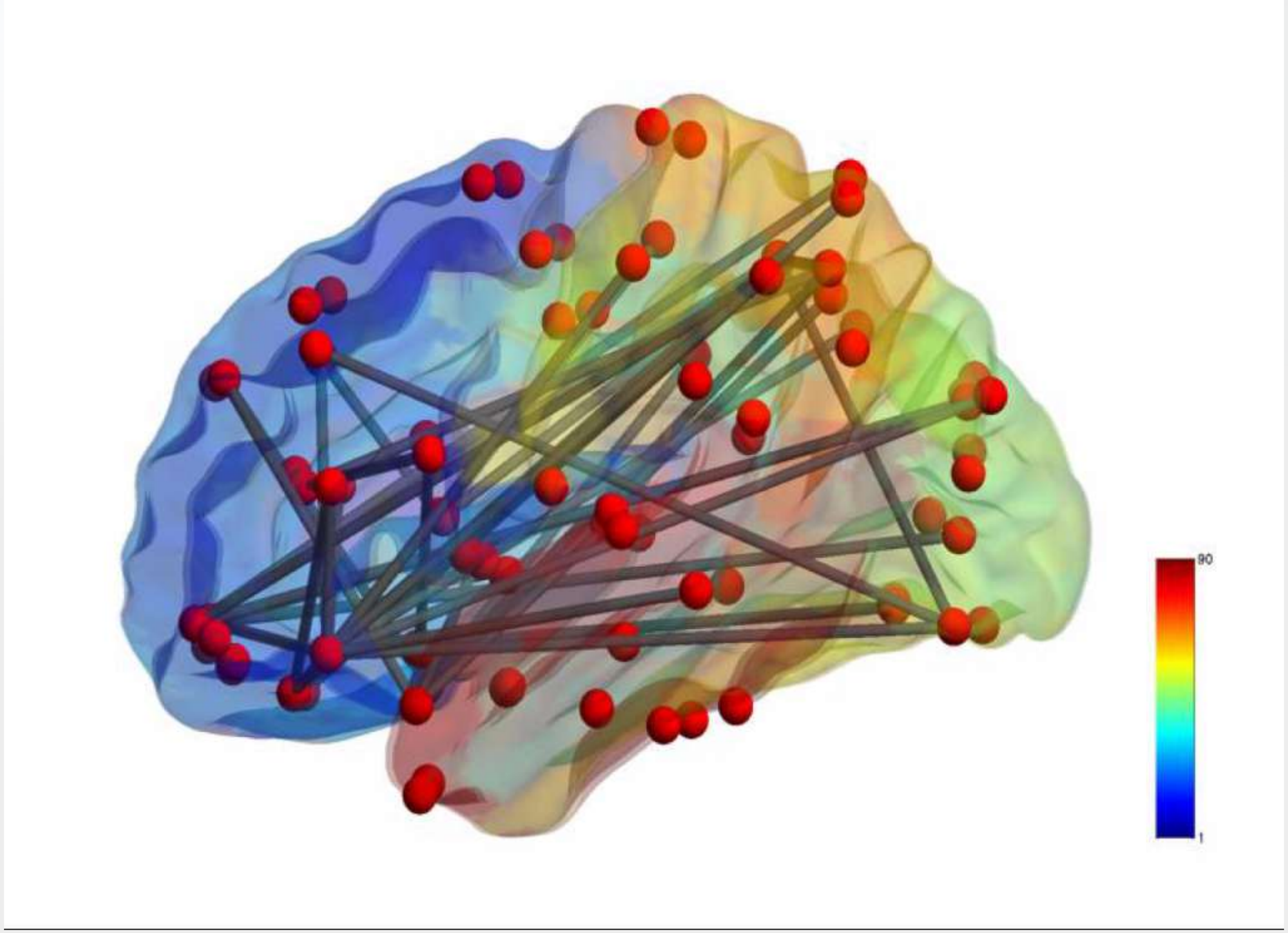
Regional Properties (Preliminary Data)

- The properties of each node or region being analyzed can be quantified.

- Can the directional properties show differences?



NBS – Expected outcome



Seed Based Analysis

- Certain regions of the brain are more susceptible to damage by HIV
- Clinical presentation of HAND has changed due to the efficacy of cART
- Primarily affects the FSTC (fronto-striato-thalamo-cortical) circuits
- Candidate seed regions
  - Basal Ganglia
  - Inferior Frontal Cortex
  - Posterior Cingulate Cortex

Expected Goals

- Novel time-series analysis methods for improved characterization of brain connectivity
- Statistical framework for analysis of network data
- Insights for improved diagnosis of HAND

Current Progress

1. **To develop and evaluate novel time-series analysis methods for exploring connectivity in high-dimensional time-series ensemble.**
    - Develop the framework utilizing state-space reconstruction and radial basis function networks, for capturing non-linear pair-wise interactions in time-series.
    - Explore the applicability of multivariate time-series analysis methods for recovery of underlying network interactions using large-scale Granger causality.
    - Systematically test and evaluate the performance of the methods for adequate recovery of underlying network structure via the use of benchmark datasets and functional MRI simulations.
2. **To model a suitable network analysis framework for identifying changes in the brain connectivity profiles.**
    - Quantitatively characterize the network profiles (at a global as well as regional level) based on graph theoretic approaches with the aim of developing imaging-derived biomarkers for disease.
    - Apply and adapt the network based statistic framework for analyzing connectivity profiles to detect edge level effects of disease.
    - Develop a statistical framework for performing seed-based connectivity in a non-linear and multivariate sense for studying whole-brain connectivity maps.
3. **To quantitatively evaluate our system in a clinical pilot study by performing an in-depth assessment of changes in resting-state brain activity in subjects with HIV infection.**
    - Preprocess and analyze clinical, neuropsychological testing and neuroimaging data acquired in a pilot study for identifying subjects with HAND based on current clinical standards.
    - Evaluate relationships between neuropsychological testing scores and connectivity derived summary measures, for assessing their applicability as clinical biomarkers.
    - Assess regional changes in brain networks occurring as a result of neural injury caused by HIV infection.

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