VISUALIZING NETWORK CONNECTIVITY *IN PARKINSON'S DISEASE*

Phoebe G. Spetsieris, PhD
Vijay Dhawan, PhD
David Eidelberg, MD

Center for Neurosciences

http://www.feinsteinneuroscience.org

Feinstein Institute for Medical Research
Northwell Health, N.Y., USA

Feinstein Institute for Medical Research
Northwell Health, USA

OBJECTIVE

Visualize and Study the Functional Sub-Network Connectivity Associated with PD using PET Parametric Images of Glucose Metabolism.

STEPS

1. **DETEMINE DISEASE SPECIFIC NETWORK PATTERNS (IMAGING BIOMARKERS) – using PCA**

2. **VISUALIZE DISEASE PC NETWORK (SUBNET) ASSOCIATED CONNECTIVITY USING GRAPH THEORETICAL CONCEPTS – using SICE**

3. **EVALUATE SUBNET BRAIN ORGANIZATION AND FUNCTION**

METHODS: Combined SSM-PCA and SICE-GLASSO Regional Network Analysis

SSM-PCA: **The Scaled Subprofile Model of Principal Component Analysis is a multivariate reduction technique that partitions group functional spatial covariance into orthogonal regionally weighted overlapping patterns corresponding to different sources of variation that may be normal, disease related, noise or outliers.**

SICE-GLASSO: **Sparse Inverse Covariance Estimation using the Graphical Lasso allows us to determine a sparse binary adjacency matrix indicating prominent topological organization of functional connectivity in brain networks.**

FOCUSED: **Apply GLASSO Estimation to SSM-PCA subnetwork data.**

Application in PD: **To visualize connectivity in Parkinson's disease**
(a neurodegenerative disorder affecting movement and cognition.)

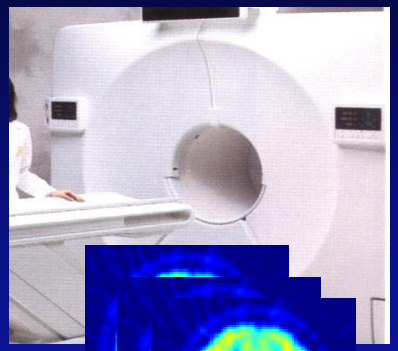
Software: MATLAB (Mathworks, Sherborn, MA), ScAnVP (http://www.feinsteinneuroscience.org/)

graphicalLasso.m , Xiaohui Chen 02/2012, UIUC, Brain Connectivity Toolbox (BCT)

Control Group

14 Healthy subjects
9m/5f , age 60.3(7.2)

PET Scanner

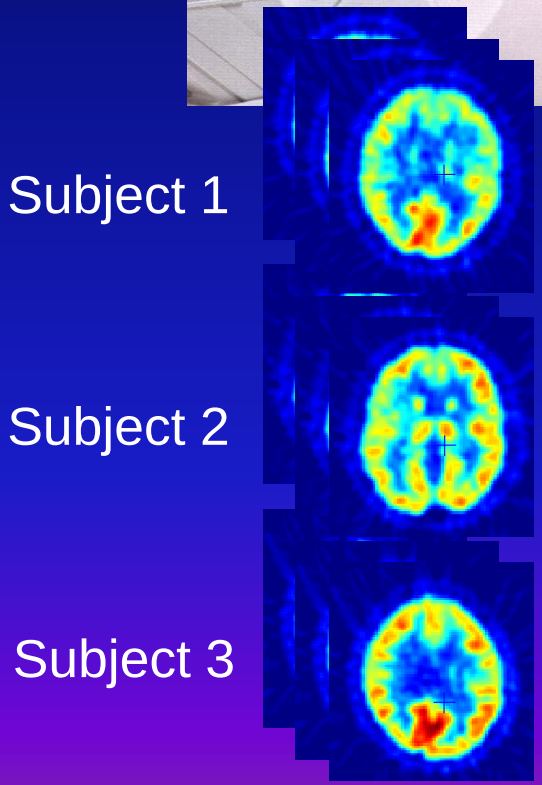


Disease Groups

Derivation 33 PD patients
22m/11f age 57.2(8.2), ddur 9.2(3.6)

Validation 14 PD patients
10m/4f , age 60.8 (6.4) ddur 1.8 (0.9)

18F-FDG PET Rest State Parametric Images of Glucose Metabolism



RAW FDG DATA SCANS

Spetsieris et al., *J Vis Exp* 2013

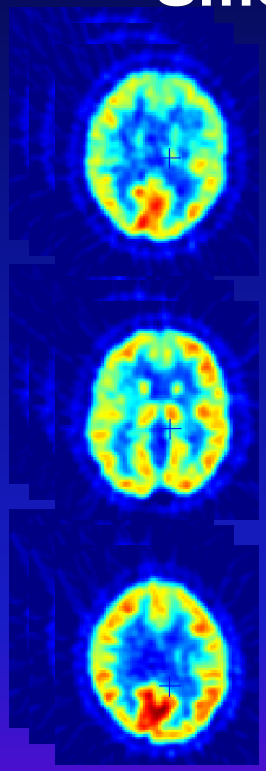
PREPROCESSING

Spatial Normalization in Stereotaxic Space and Smoothing*

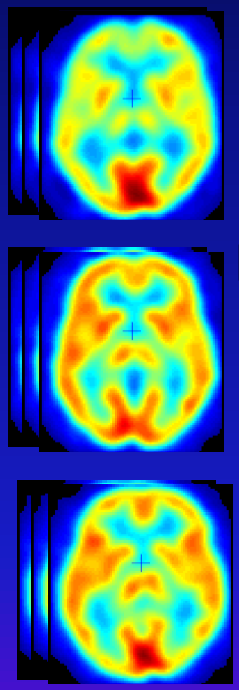
Subject 1

Subject 2

Subject 3

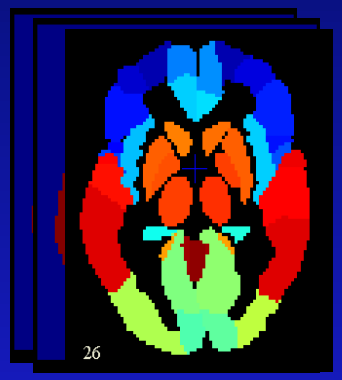


RAW



NORMALIZED
SMOOTHED
79x95x69 vox

Regional Segmentation



AAL Atlas
95 ROIS

Mean Regional Values

D

DATA MATRIX
33 x 95
Sub x Rois

*SPM, *Statistical Parametric Mapping*, UCL

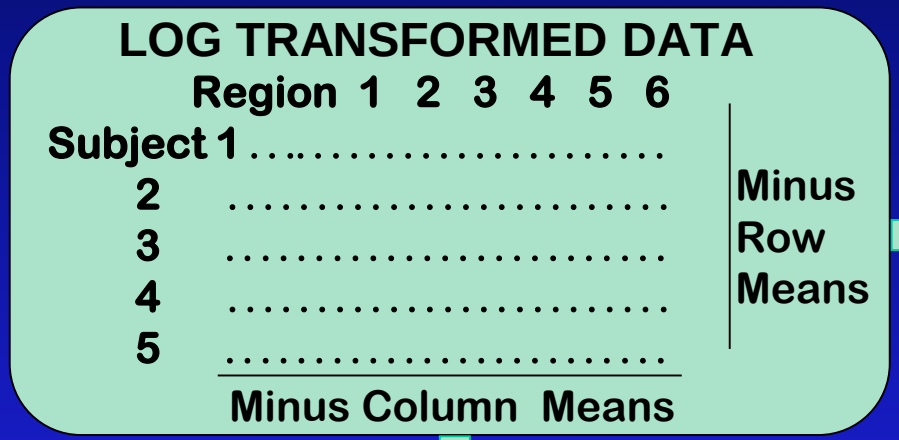
DATA PREPROCESSING

Log Transformation

Row and Column Centering of Data Matrix

D

Subject by Region Group Data Matrix
33 Subjects
95 Region Mean Values

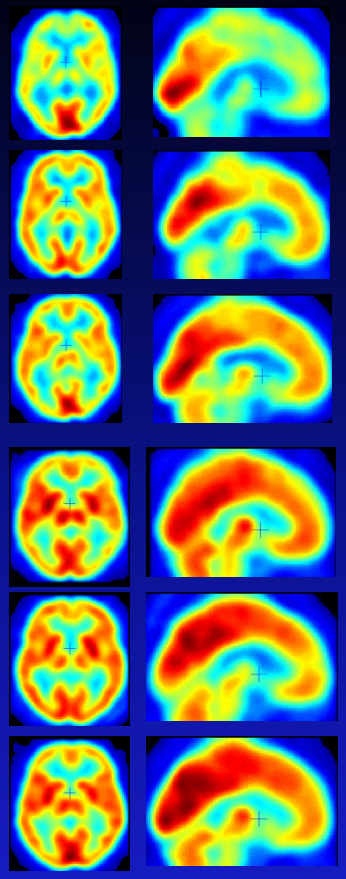


2. GLASSO SICE

1. SSM PCA

Spetsieris et al., *J Vis Exp* 2013

1. SSM-PCA



33Subjects

1

2

3

4

5

6

D

Group Data Matrix (33x95)

COVARIANCE MATRIX (95x95)

ROI 1 2 3 4 5 . .

ROI 1 2 3 4 5 .

. . $C_{rr'}$ . .

$\Sigma_j (D_{jr} \times D_{jr'})$

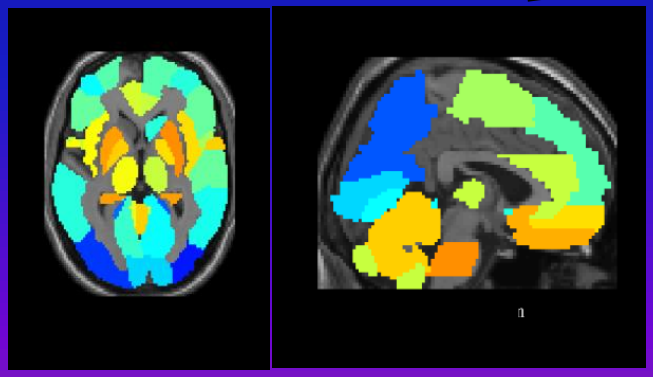
. . . . .

PCA

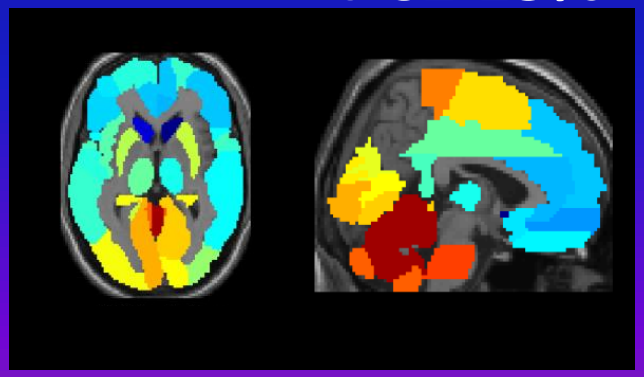
PC3, PC4...

PC1 34% vaf

PC2 15%



PC1 Pattern Map



PC2 Pattern Map

1. SSM-PCA

SCALED SUBPROFILE MODEL - PRINCIPAL COMPONENT ANALYSIS

- PCA is performed on the covariance matrix of the normalized and centered data $\mathbf{D}$ to derive a complete set of orthogonal Principal components $\mathbf{PC_k}$ and corresponding subject scores $\mathbf{Score_{jk}}$.
- The portion $\mathbf{D_{jk}}$ of the subject **j** data that is attributed to a specific Principal Component $\mathbf{PC_k}$ is equal to the PC times the subject Score.
- Prospective subjects can be tested by evaluating their expression scores as inner products of their data vector and the pre-derived PC pattern.

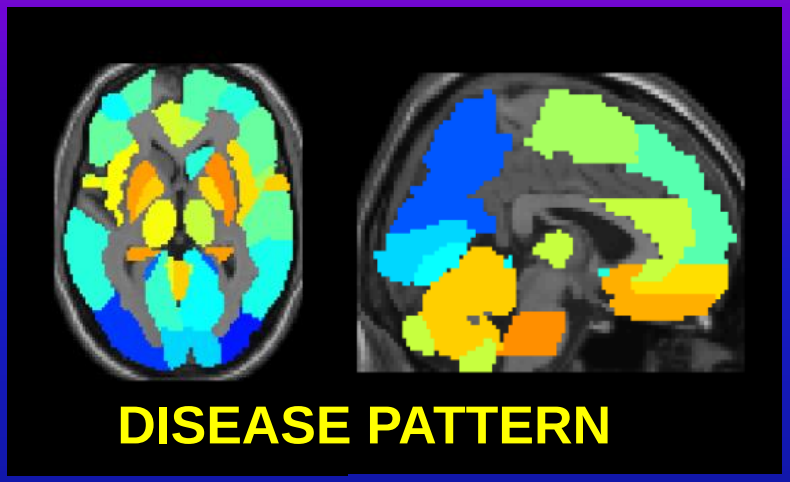
$$\mathbf{D_j} = \Sigma_k \mathbf{D_{jk}} \quad \textbf{(Whole Brain Data)} \quad (1)$$

$$\mathbf{D_{jk}} = \mathrm{Score_{jk}} \times \mathbf{PC_k} \quad \textbf{(Subnet Data)} \quad (2)$$

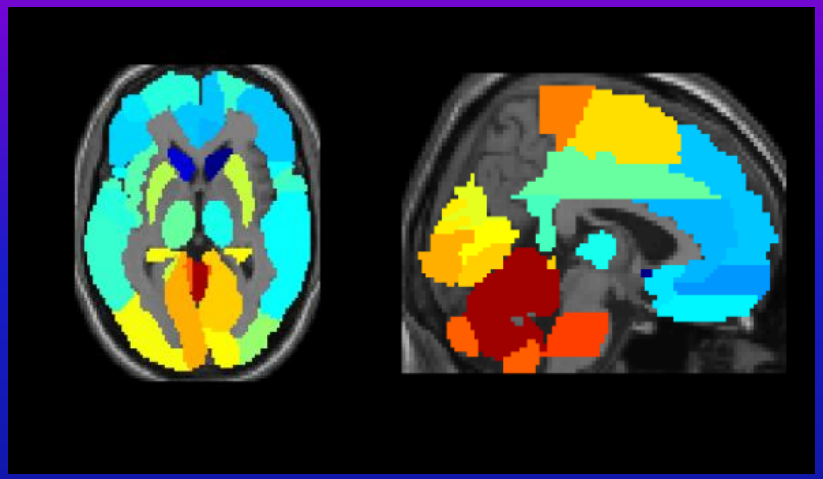
$$\mathrm{Score_{jk}} = \mathbf{D_j^T} \cdot \mathbf{PC_k} \quad \textbf{(Subject Score)} \quad (3)$$

Software: ScAnVP (http://www.feinsteinneuroscience.org/)

PC1 Pattern Map



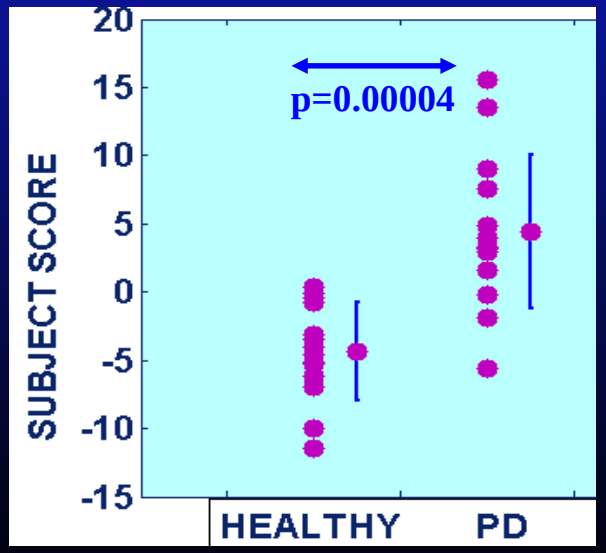
PC2 Pattern Map



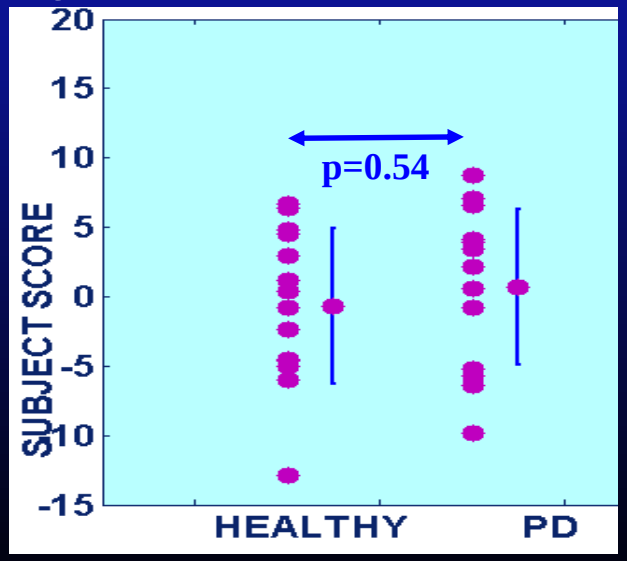
Prospective Group Expression Scores

PC1 discriminates Patients from Controls

PC1



PC2



2. GLASSO-SICE

GRAPHICAL LASSO-SPARSE INVERSE COVARIANCE ESTIMATION

S = Empirical covariance matrix, $\Theta=\Sigma^{-1}$, Inverse covariance matrix

- Use algorithm—the *graphical lasso** …to estimate sparse undirected graphical models through the use of *L1 (lasso) regularization.* Increase the variable *ρ penalty to increase sparsity of* Σ^{-1}.
- If the *ij*th component of Σ^{-1} is zero, then regions *i* and *j* are conditionally independent otherwise they are partially connected, i.e. directly functionally correlated.
- *M*aximize the penalized Gaussian log-likelihood of the data :

$$\log\det\Theta - \mathrm{tr}(S\Theta) - \rho||\Theta||_1,$$

tr denotes the trace and $||\Theta||_1$ is the L_1 *norm*—the sum of the absolute values of the elements of Σ^{-1}.

*JEROME FRIEDMAN et. al, *Biostatistics (2008),*
Software: graphicalLasso.m , Xiaohui Chen 02/2012, UIUC

2. GLASSO-SICE

APPLICATION

- Determine the binary 0/1 adjacency matrix A from Θ at maximum sparsity for fully connected graphs.
- Visualize whole brain and subnetwork connectivity.
- Examine Graph Parameters of matrix A including Sparsity and Centrality Measures (Degree, Eigenvector, Betweeness, Clustering)
- Compare Centrality vectors with PC vectors derived using ROI based SSM-PCA of the subject data and assess primary hubs.

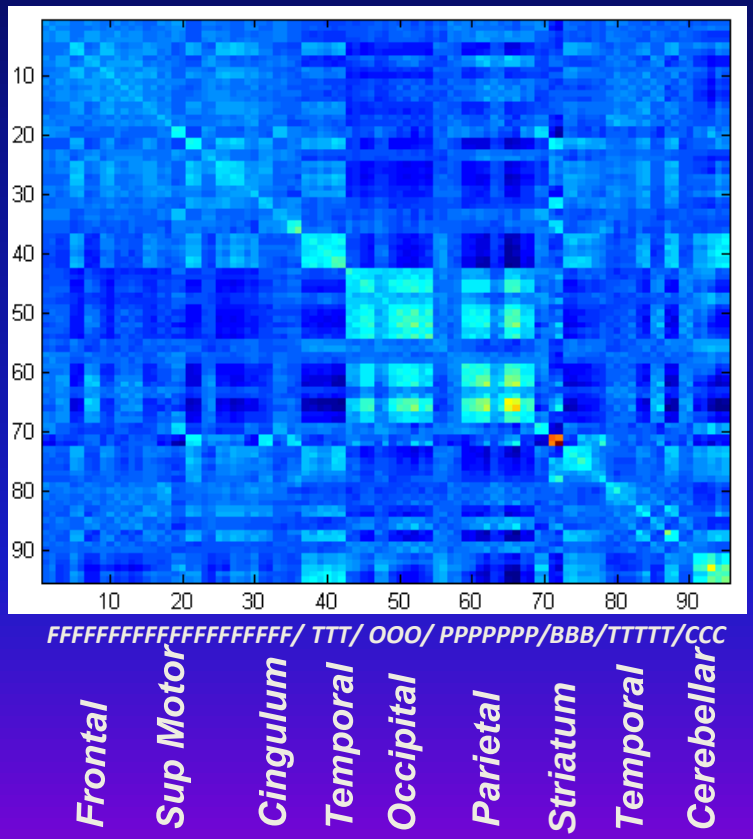
Software: Brain Connectivity Toolbox (BCT) & ScAnVP in-house

GLASSO SICE WHOLE BRAIN ADJACENCY MATRIX

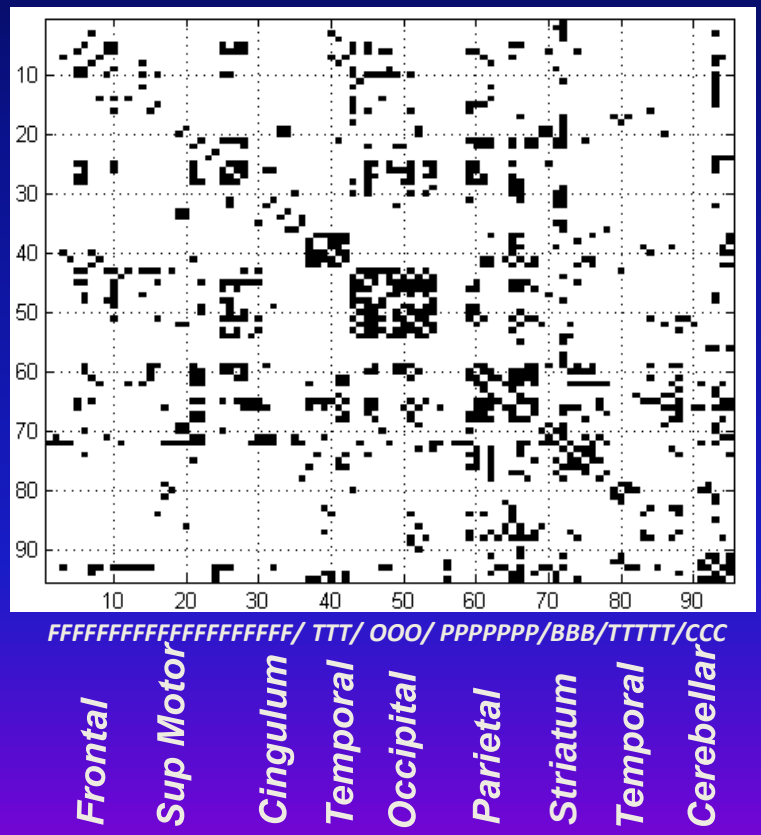
MAXIMUM SPARSITY, PD33, 95 ROIs,

ρ =0.00097, 89.2%, 483 Edges

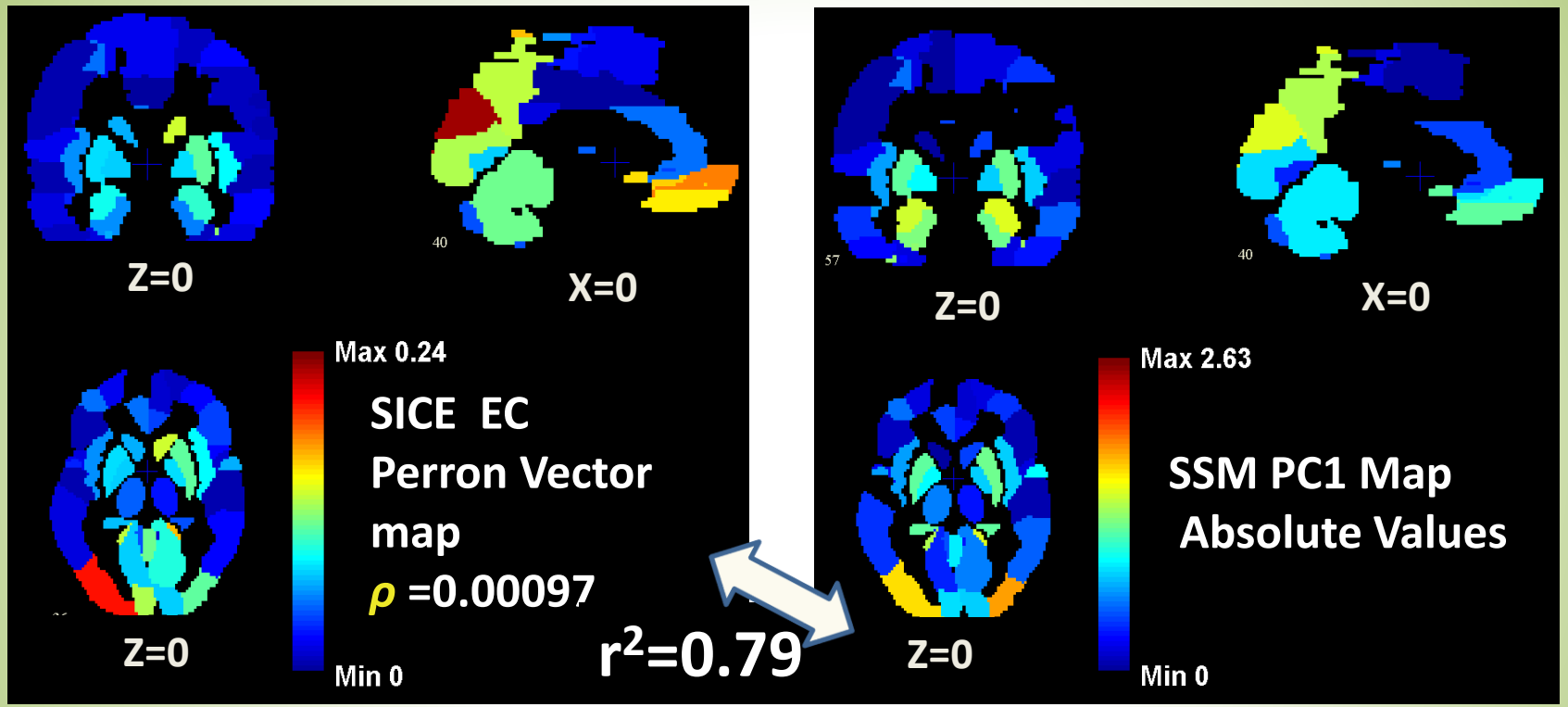
Covariance Matrix



Adjacency Matrix



EC (PERRON) VECTOR– ABS. SSM PC1 CORELLATION (33 PD patients – 95 ROIs)



EC: Eigenvector Centrality
(Primary PC of Adjacency Matrix)
483 Edges, 89.2% sparsity,10.8% density

PC1: Primary PC of Covariance Matrix

Pearson's Corr PD33abs, Vec EC00097: $r=0.84$, $r^2=0.71$, $p<0.001$ (ROI vector)

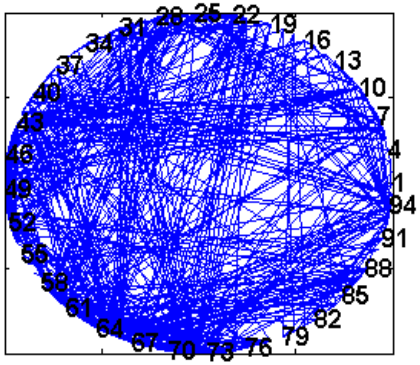
ROI Map correlation ($r=0.89$, $r^2=0.79$, $p<0.001$) (voxel)

Whole Brain 95 ROI 3D Plot.

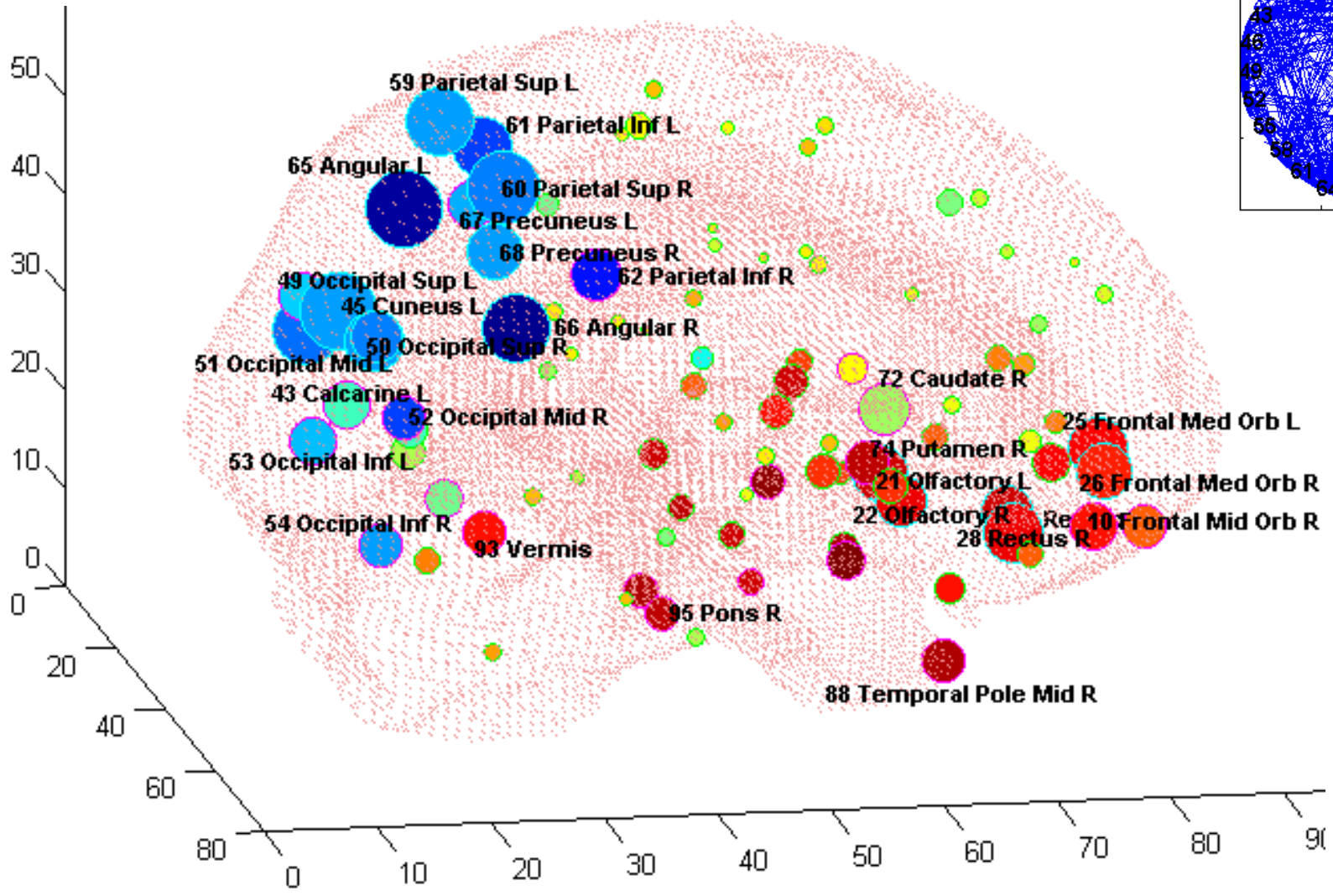
Diameter determined by EC weight

Color determined by PD33 SSM PC1 weight

89.2%
Sparsity



483 Edges

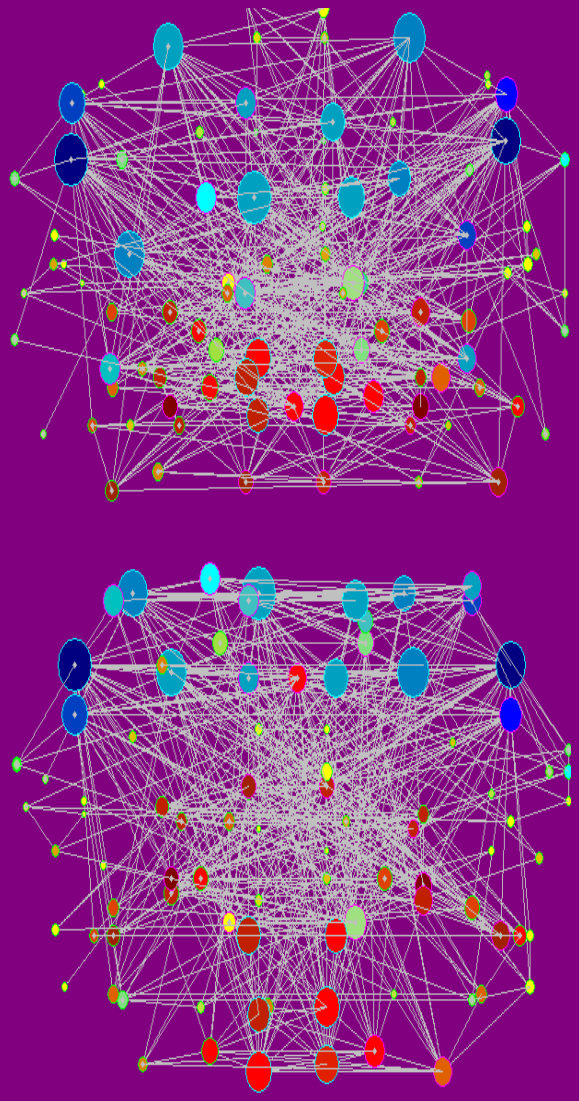


Max
1.54

SSM-PC
Region
Weight

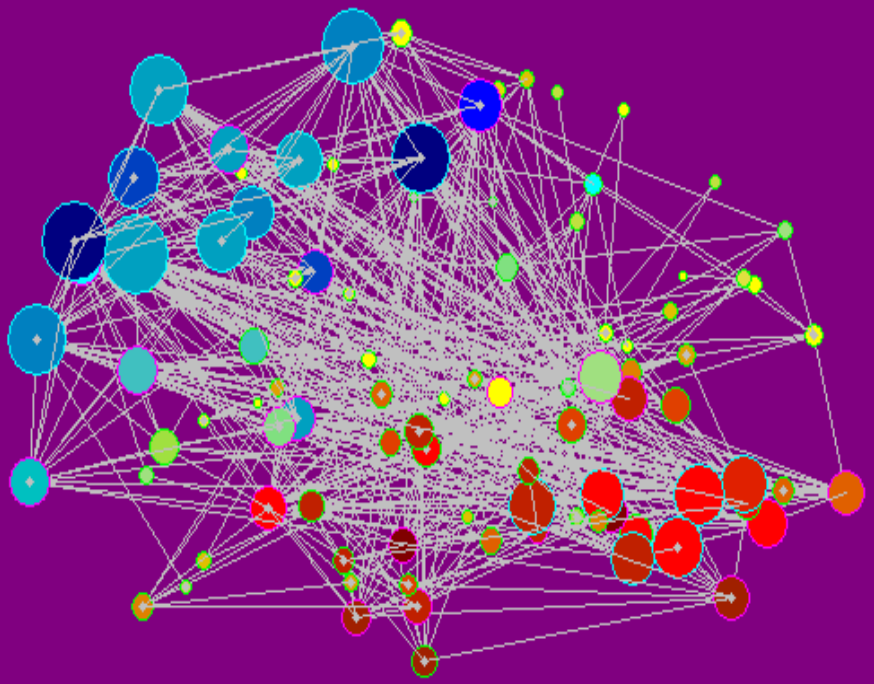
Min -
2.63

Whole Brain 95 ROI Connectivity



Diameter determined by EC

Color determined by PD33 SSM PC1



Max
1.54

Min
-2.63

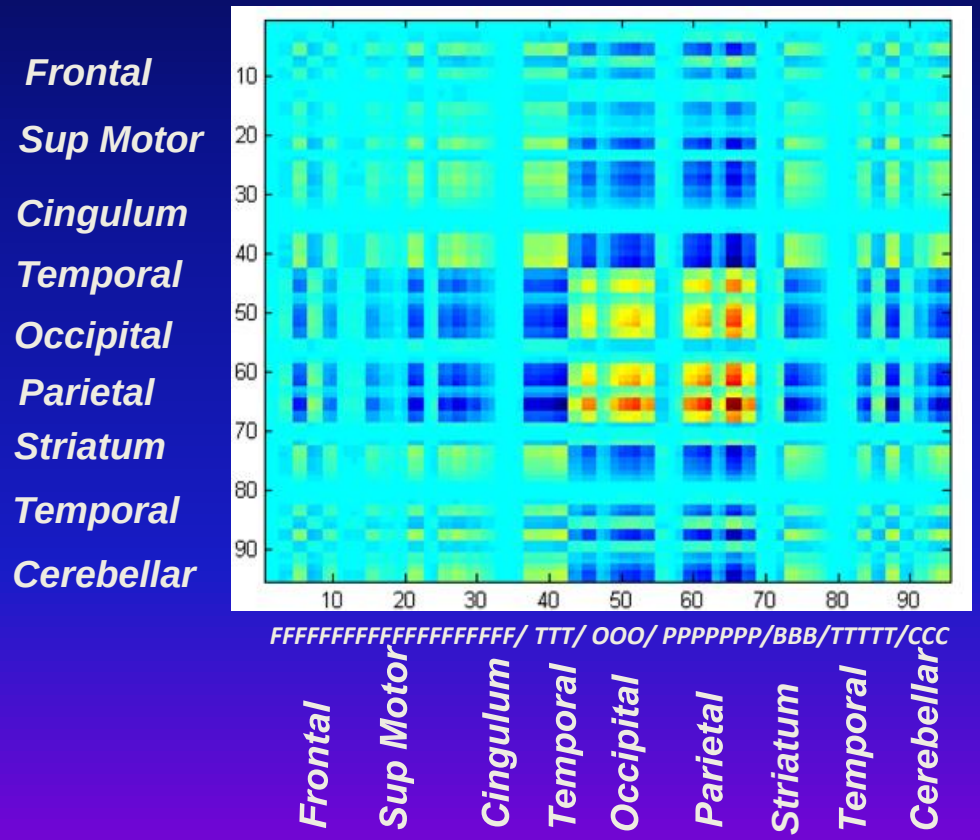
GLASSO SICE SSM PC1 SUBNET ADJACENCY

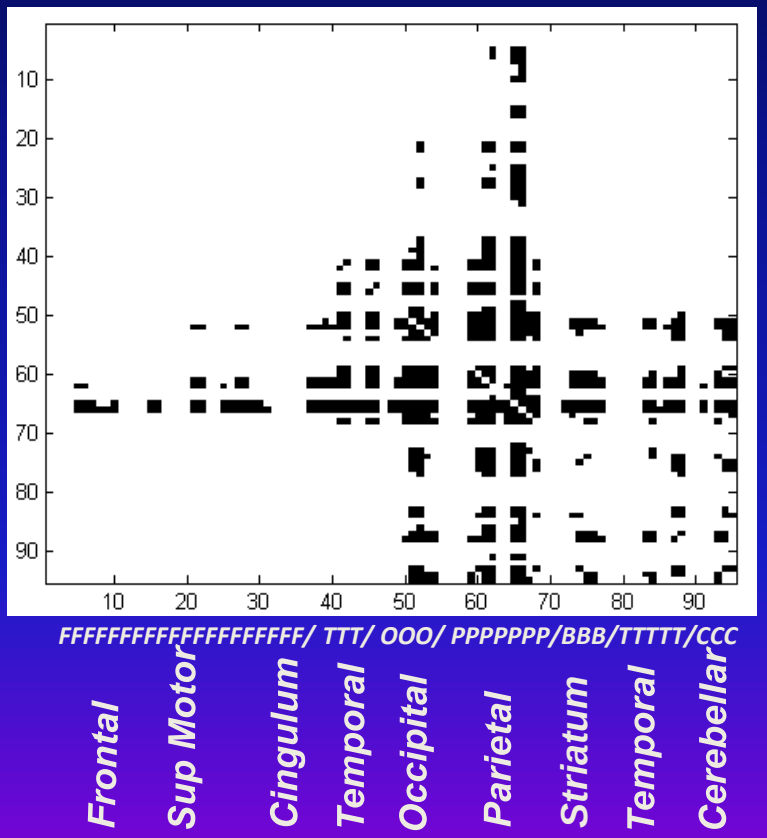
PD33, 60 ROI Connected Subnetwork

ρ =0.001, 80.6%, 343 Edges (92.2% of whole brain)

Covariance Matrix

Adjacency Matrix

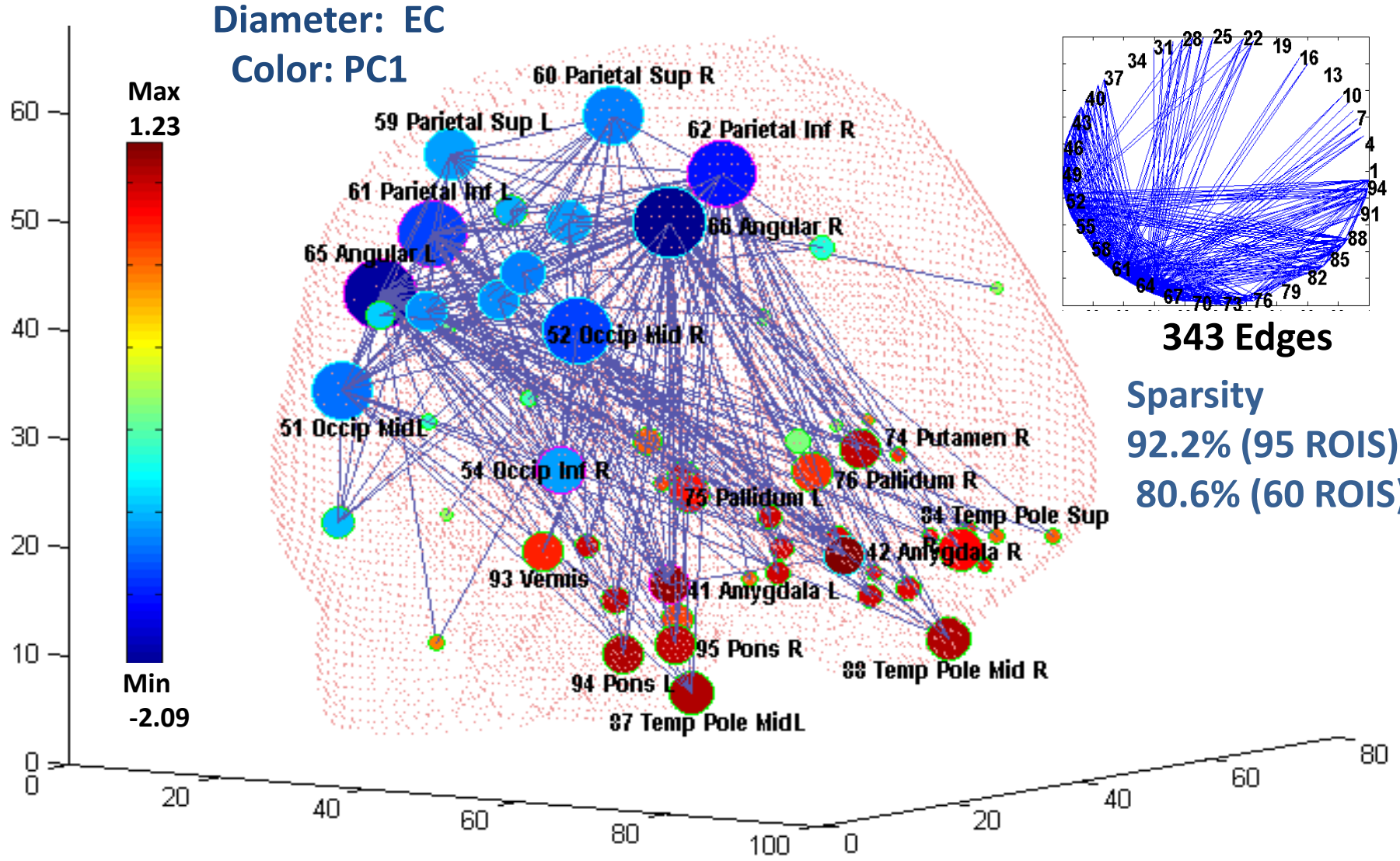




60 ROI SSM PC1 Subnet Connectivity

FRONTAL DISCONTINUITY IN 95 ROI CONFIGURATION
SUBNET OF 60 ROIS IS FULLY CONNECTED.

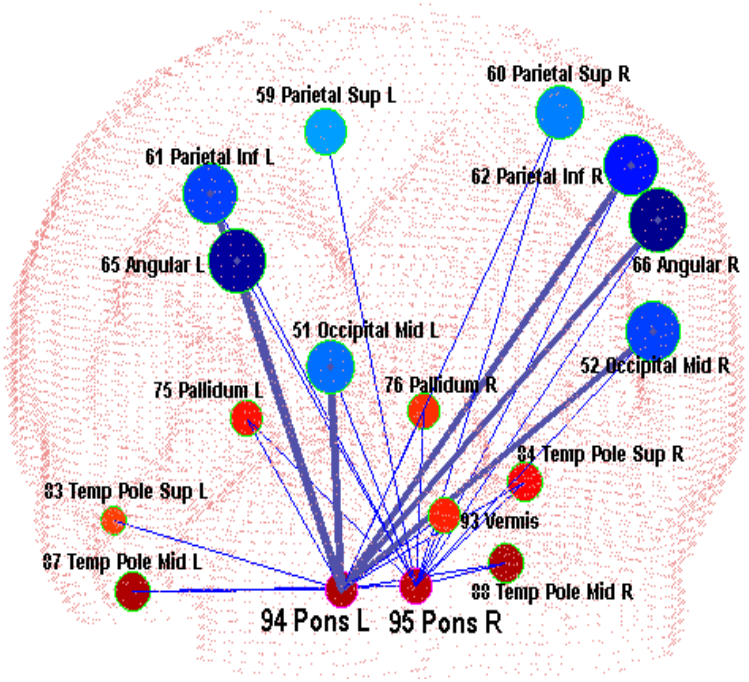
Three dimensional plot depicts 257 maximally weighted bootstrapped edges.



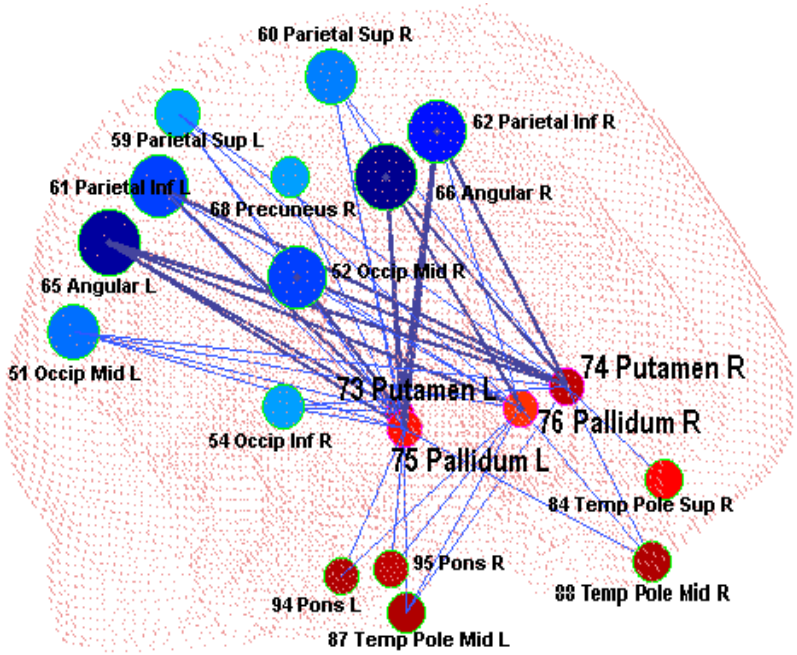
60 ROI SSM PC1 SUBNET

Partial functional connections of the bilateral Pons (Left) and of the Putamen/Pallidum (Right) within the 60 ROI subnet. Bold lines depict the highest bootstrap weighted connections.

Pons

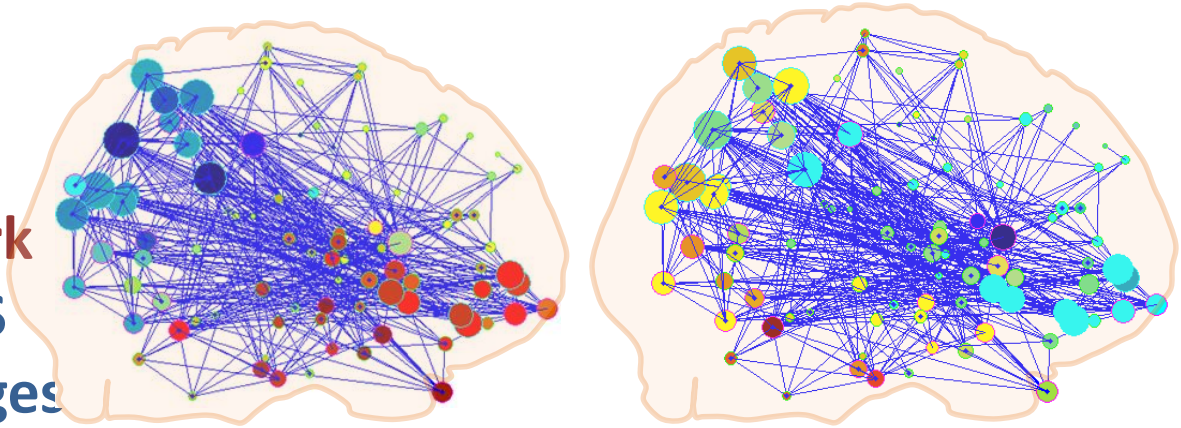


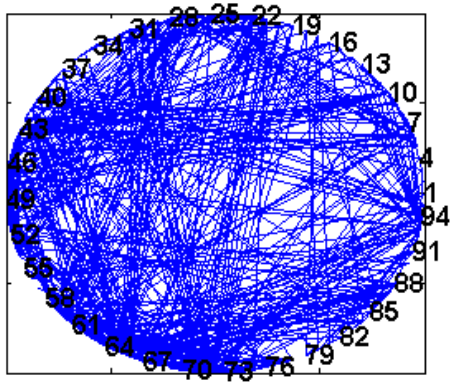
Putamen/Pallidum



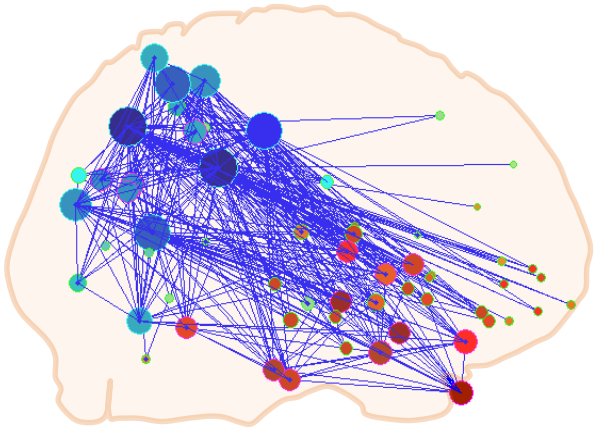
Whole Brain and Subnet Connectivity

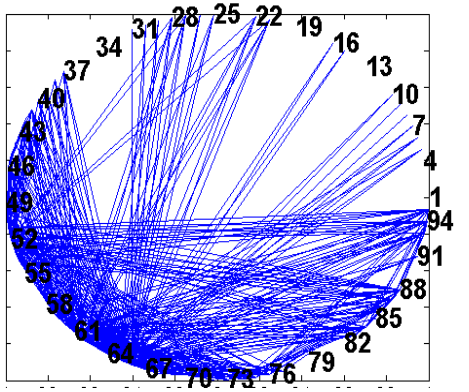
Whole Brain Network
95 ROIS
483 Edges



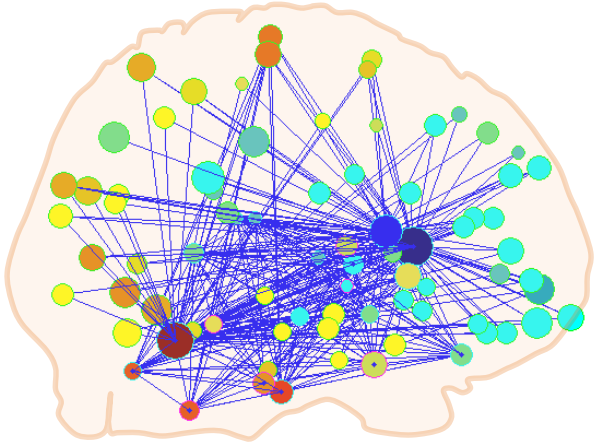


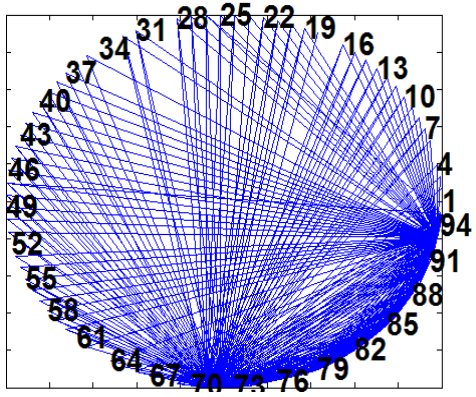
SSM_PC1 Subnet
60 ROIS
343 Edges





SSM_PC2 Subnet
80 ROIS
349 Edges





CONCLUSION

SSM-PCA and SICE are different methods of reducing covariance data to essential elements.

PCA is a simpler and more direct approach for identifying disease specific patterns (imaging biomarkers) and providing corresponding subject scores of disease expression.

SICE provides greater insight into the more prominent underlying topographical structure of the data but does not directly distinguish between disease related and normal connectivity.

A new more focused approach of applying SICE to PCA derived disease specific partitions of the data may enhance visualization and comprehension of functional associations in neurodegenerative diseases of the brain.

Acknowledgment

- **Thomas Chaly, PhD** — *Radiochemistry*
- **Yilong Ma, PhD** — *BioMedical Physics*
- **Chishun Peng, PhD** — *Computer Science*
- **Michael Small, MS** — *Technical Support*
- **Chris Tang, M.D., PhD** — *Statistical Neuroscience*

This work was partially supported by the National Institutes of Health P50 NS 38370 and R01 NS 35069.

References

- J. Friedman, C.D. T. Hastie, and R. Tibshirani, "Sparse Inverse Covariance Estimation With The Graphical Lasso," *Biostatistics*, vol. <9>, no. <3>, pp. <432-441>, 2008.
- D. Eidelberg, "Metabolic brain networks in neurodegenerative disorders: a functional imaging approach," Trends in Neurosciences, vol. 32, no. 10, pp. 548-57, 2009.
- Spetsieris P, Eidelberg D. Scaled subprofile modeling of resting state imaging data in Parkinson's disease: Methodological issues," NeuroImage; 54(4):2899-914, 2011.

pspetsie@northwell.edu