VISUALIZING NETWORK CONNECTIVITY IN PARKINSON’S DISEASE

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OBJECTIVE

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

STEPS

1. DETERMINE 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)

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

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

LOG TRANSFORMED DATA

Region 1 2 3 4 5 6
Subject 1 .......................... Minus Row Means
2 .................................
3 .................................
4 .................................
5 .................................

Minus Column Means

1. SSM PCA

2. GLASSO SICE

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

Spetsieris et al., J Vis Exp 2013
1. SSM-PCA

**COVARIANCE MATRIX (95x95)**

\[
\Sigma_j (D_{jr} \times D_{jr'})
\]

\[
\begin{array}{cccccc}
0 & C_{rr'} & 0 & \cdots & 0 \\
C_{rr'} & 0 & \cdots & 0 & 0 \\
0 & \cdots & 0 & 0 & 0 \\
\end{array}
\]

**Group Data Matrix (33x95)**

**PCA**

- PC1 34% vaf
- PC2 15%
- PC3, PC4...

**33 Subjects**

1
2
3
4
5
6

**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 $D$ to derive a complete set of orthogonal Principal components $PC_k$ and corresponding subject scores $Score_{jk}$.
- The portion $D_{jk}$ of the subject $j$ data that is attributed to a specific Principal Component $PC_k$ 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.

$$D_j = \sum_k D_{jk} \quad \text{(Whole Brain Data)} \quad (1)$$

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

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

Software: ScAnVP (http://www.feinsteinneuroscience.org/)
PC1 Pattern Map

PC2 Pattern Map

DISEASE PATTERN

Prospective Group Expression Scores

PC1 discriminates Patients from Controls

PC1

PC2

p=0.00004

p=0.54
2. GLASSO-SICE

GRAPHICAL LASSO-SPARSE INVERSE COVARIANCE ESTIMATION

\[ S = \text{Empirical covariance matrix}, \quad \Theta = \Sigma^{-1}, \text{Inverse covariance matrix} \]

- Use algorithm—the graphical lasso* ...to estimate sparse undirected graphical models through the use of \( L_1 \) (lasso) regularization. Increase the variable \( \rho \) penalty to increase sparsity of \( \Sigma^{-1} \).

- If the \( ij \)th component of \( \Sigma^{-1} \) is zero, then regions \( i \) and \( j \) are conditionally independent otherwise they are partially connected, i.e. directly functionally correlated.

- Maximize the penalized Gaussian log-likelihood of the data:

  \[
  \log \det \Theta - \text{tr}(S\Theta) - \rho \| \Theta \|_1 I, \\
  \]

  \( \text{tr} \) denotes the trace and \( \| \Theta \|_1 \) is the \( L_1 \) norm—the sum of the absolute values of the elements of \( \Sigma^{-1} \).

*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 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, Betweenness, 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,
\( \rho = 0.00097 \), 89.2%, 483 Edges

Covariance Matrix

Adjacency Matrix

Frontal  Sup Motor  Cingulum  Temporal  Occipital  Parietal  Striatum  Temporal  Cerebellar

Frontal  Sup Motor  Cingulum  Temporal  Occipital  Parietal  Striatum  Temporal  Cerebellar
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
\( \rho = 0.001, 80.6\%, 343 \text{ Edges (92.2\% of whole brain)} \)

Covariance Matrix

Adjacency Matrix

Frontal
Sup Motor
Cingulum
Temporal
Occipital
Parietal
Striatum
Temporal
Cerebellar
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.

Diameter: EC

Color: PC1

Sparsity
92.2% (95 ROIS)
80.6% (60 ROIS)
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.
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.
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References

