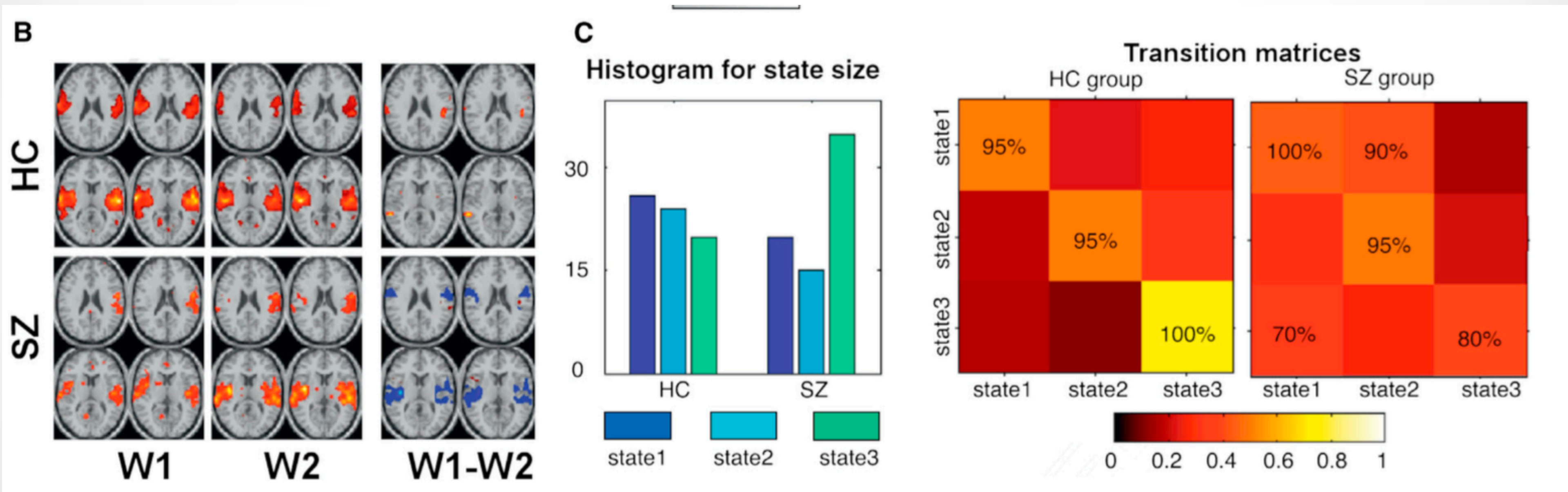
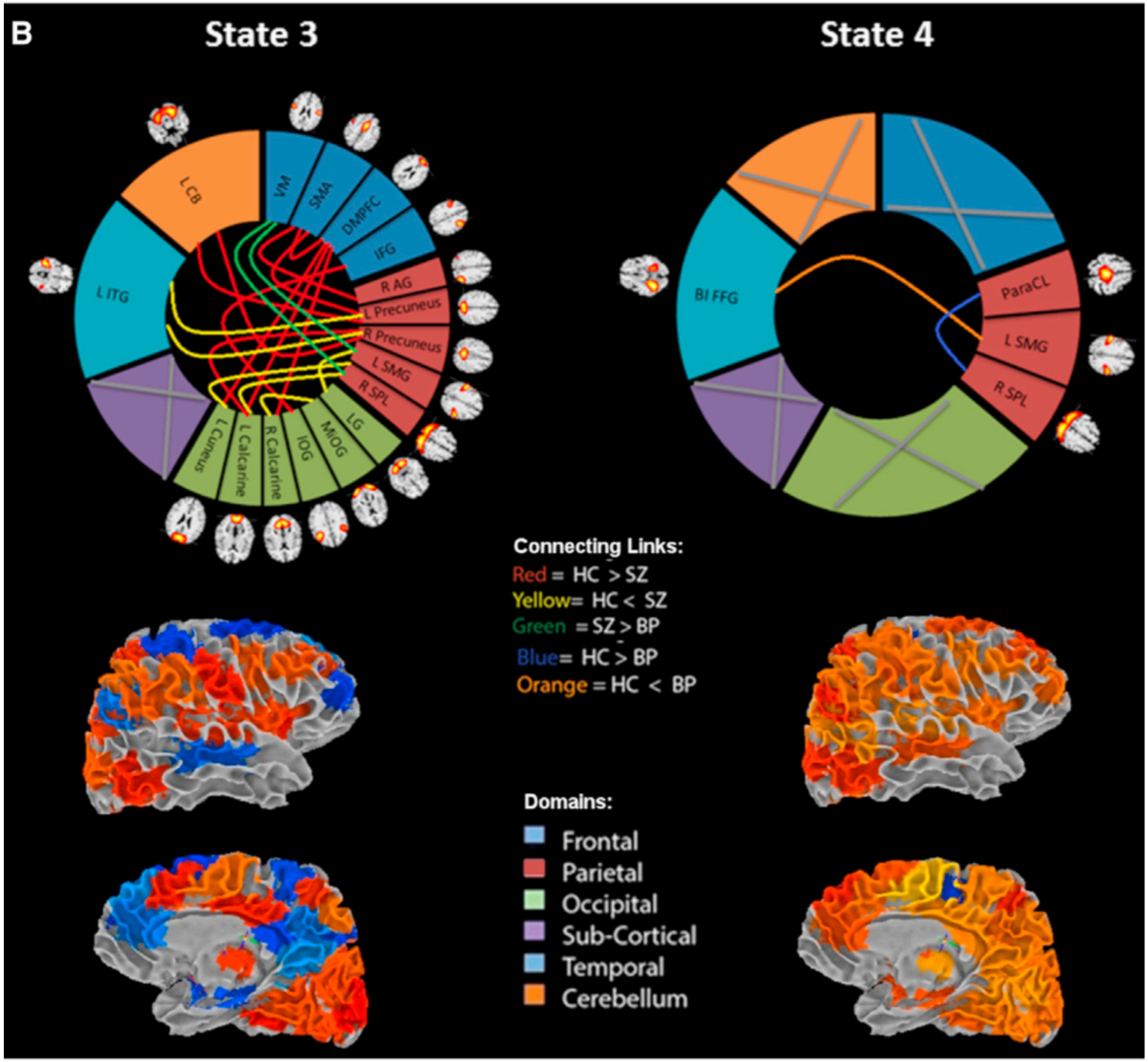
Time-Varying Functional Connectivity

Sanmi Koyejo
Stanford University & University of Illinois



Dynamics of Schizophrenia vs. healthy controls
(Calhoun et. al., 2015)



Dynamics of Schizophrenia vs. Bipolar vs. healthy controls (Calhoun et. al., 2015)

Motivating Questions

- How are the regions of the brain functionally connected?
- How do these connections change over time?
- …

- How are the changing connections related to behavior, disease, etc.?

Main Steps

Node Extraction

- Voxels
- ROI
- ICA

Connectivity Measure

- Correlation
- Precision
- Mutual information
- MTD

Time-Varying Evolution

- Nonparametric
- Parametric

Estimation & Summary

- State estimation & description
- Cartographic profiling

Inference

- Parametric
- Nonparametric (e.g. VAR)

Highlights

- Estimation of time-varying functional connectivity
    - Parametric vs. non-parametric techniques
- Techniques for summarizing results
- Techniques for inference

- Will not cover:
    - Node extraction: Voxels vs. ICA vs. ROI
    - Techniques for selecting model hyper-parameters
    - Selecting the connectivity measure
    - Some signal processing techniques e.g. IVA (Ma et. al., 2014)

Important to Remember

"All models are wrong but some are useful"

- George Box

- In general, models are statistical summaries, and are useful to the extent that the elucidate important properties of the brain
- Thus, these techniques are not "how the brain works" i.e. none of these models are "correct"

Estimating Time-Varying Functional Connectivity

- Non-parametric
  - Kernel / Sliding Window
  - Change points
- Parametric
  - DCM
  - Latent variable model (e.g. HMM)

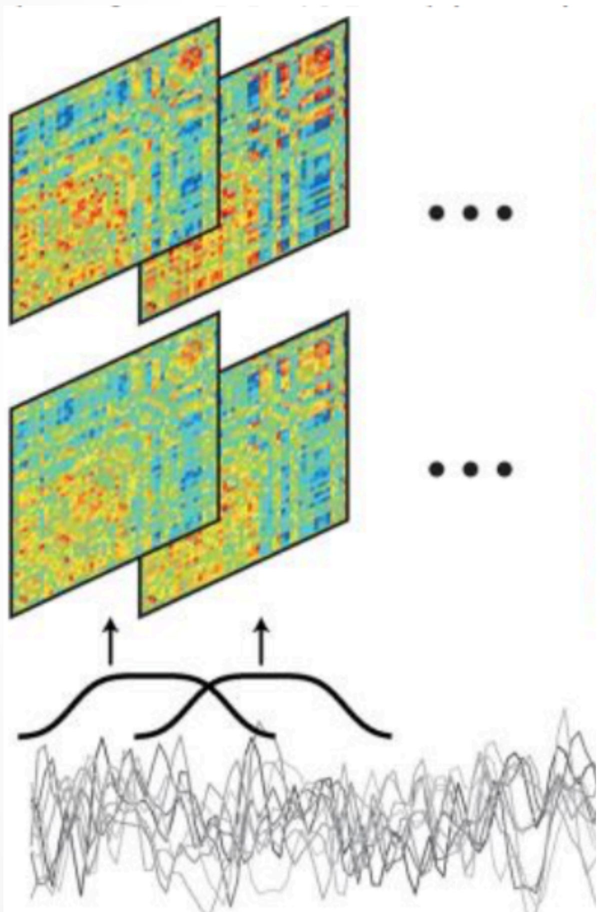
Outline

- ~~Introduction~~
- **Non-parametric temporal evolution**
- Parametric temporal evolution
- Summary measures
- Inference
- Summary

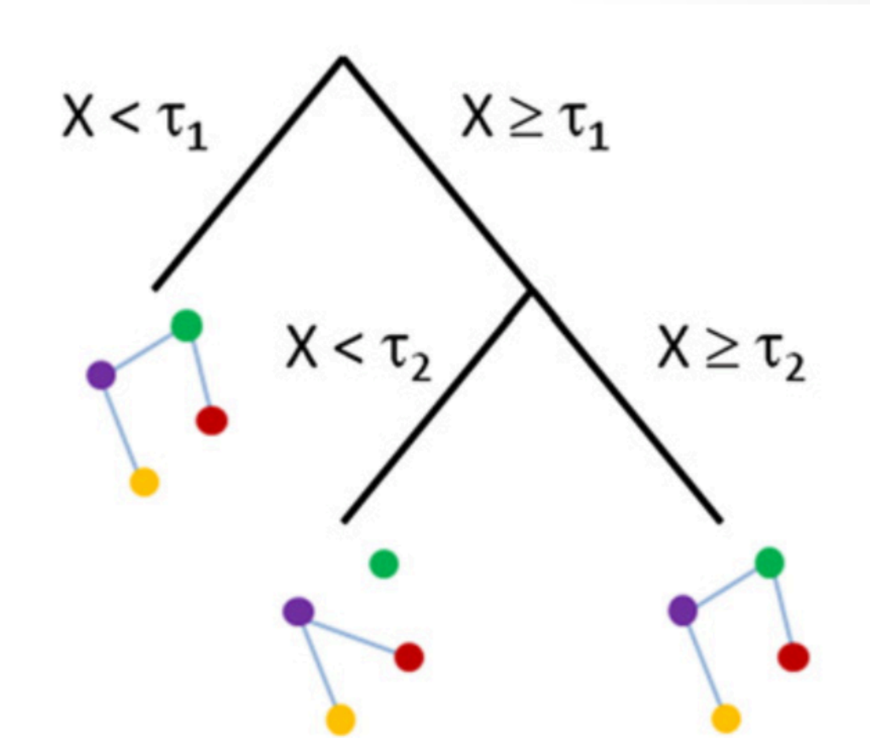
Part 1

Non-parametric temporal variation

Nonparametric Approach for Temporal Evolution



Rashid et. al. (2014)



Cribben et. al. (2012)

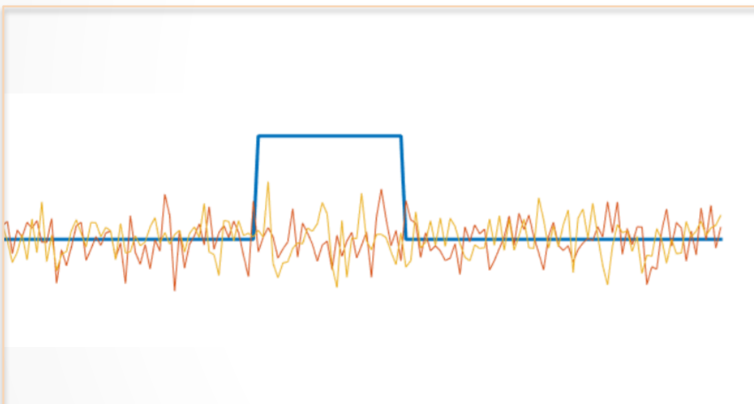
(Kernel) Sliding Window

$$C^{i,j}(n) = FC(y^i_{n-m:n}, y^j_{n-m:n})$$

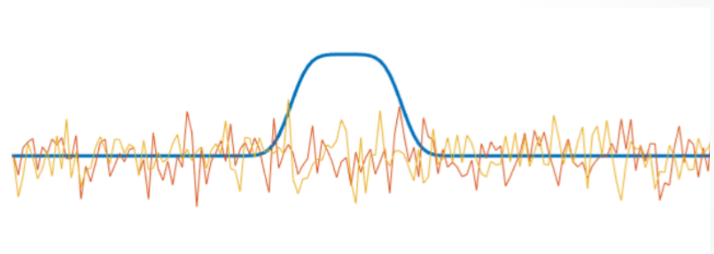
- FC = measure of functional connectivity
- C(n) = connectivity estimate at each time point "n"
- E.g. kernel smoothed sliding window correlation (after subtracting mean)

$$C^{i,j}(n) = \frac{\sum_{s=n-m}^{n} k(s-n) y^i_s y^j_s}{\sqrt{\left(\sum_{s=n-m}^{n} k(s-n) y^i_s\right)\left(\sum_{s=n-m}^{n} k(s-n) y^j_s\right)}}$$

Sliding Window Kernels

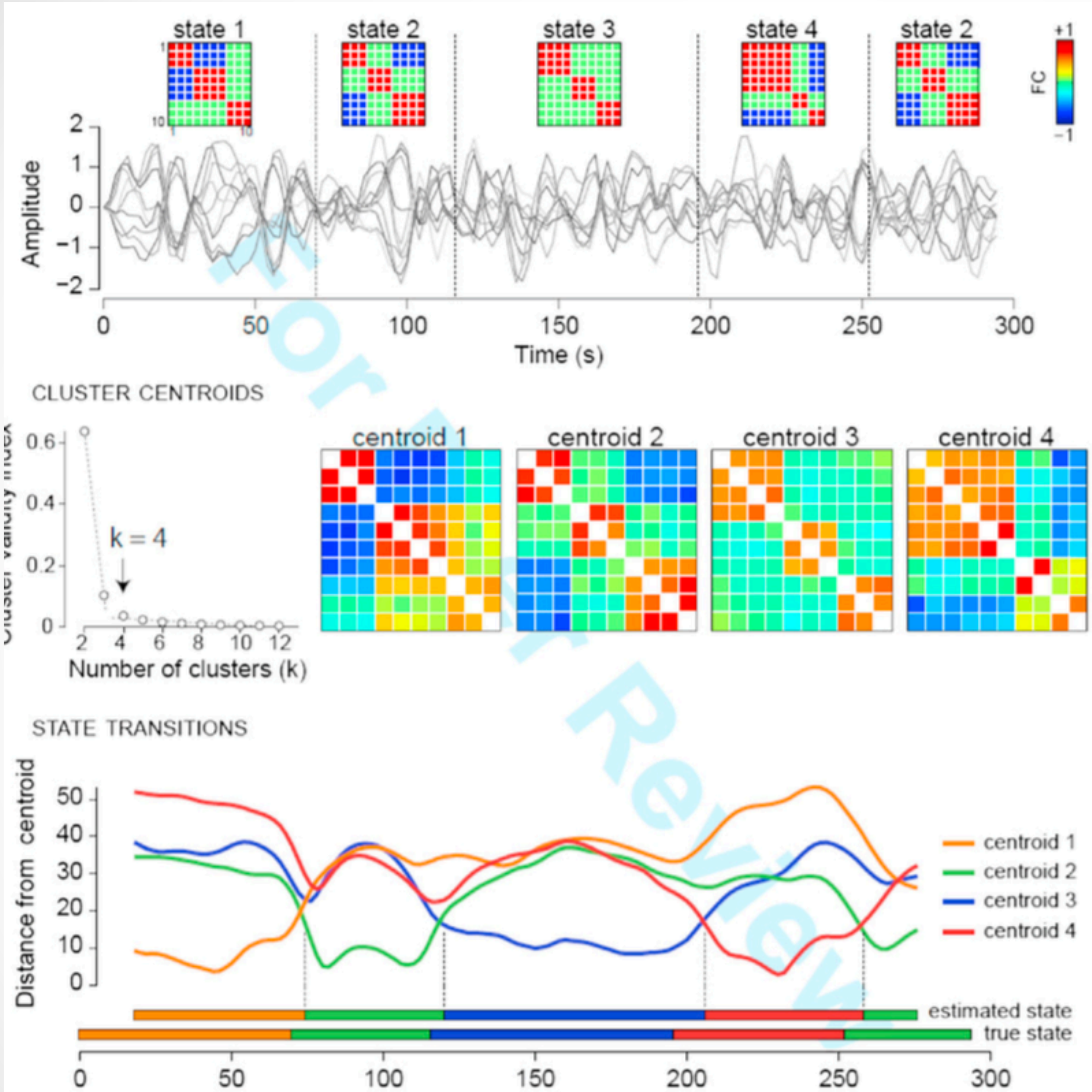


Uniform kernel



Gaussian kernel

Lindquist (2014)



Simulated time-varying Connectivity (SimTB toolbox)

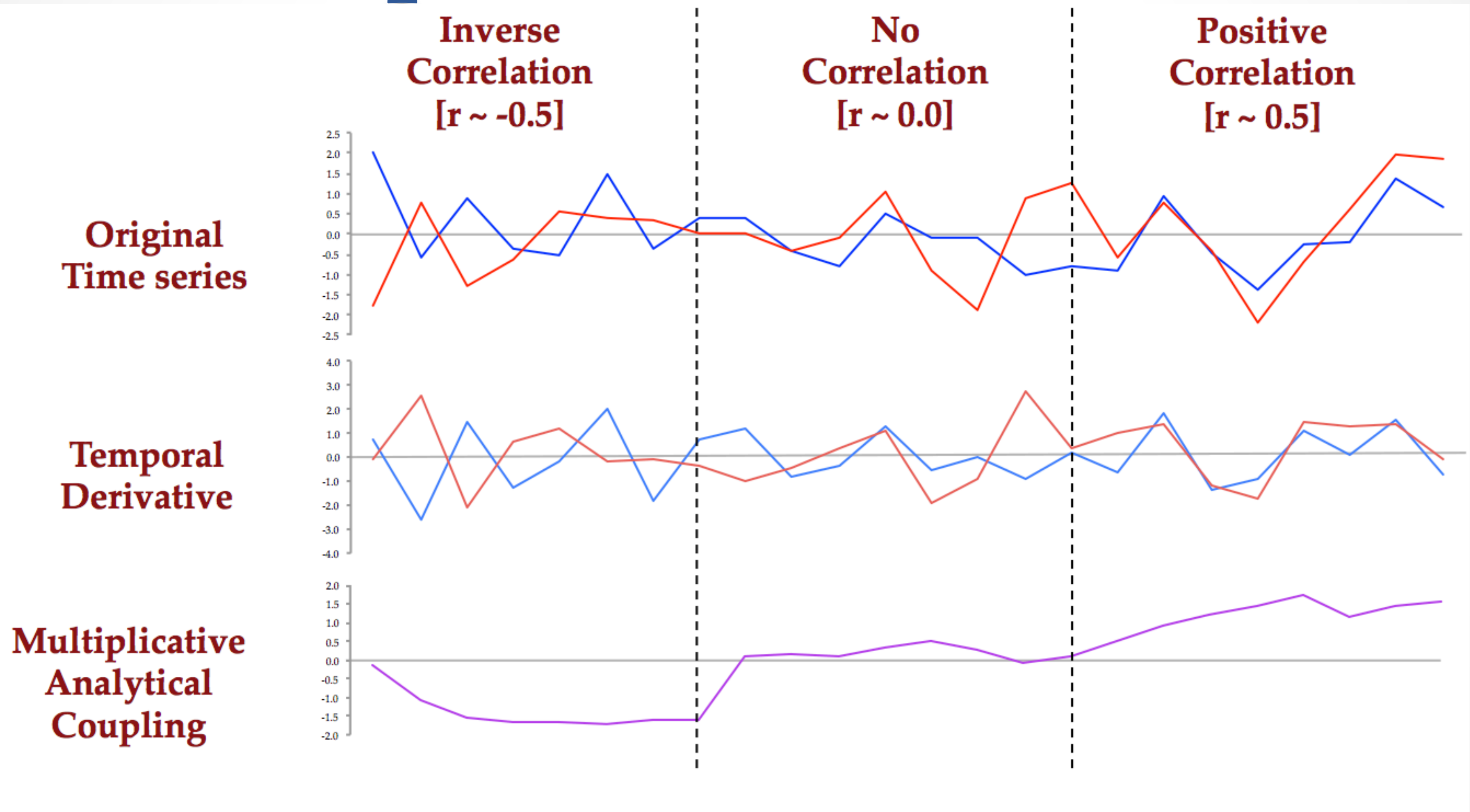
Calhoun et. al. (2015)

Connectivity Measures

- Pearson / Spearman Correlation
- Partial correlation
- Mutual information
- Multiplication of temporal derivatives (MTD)

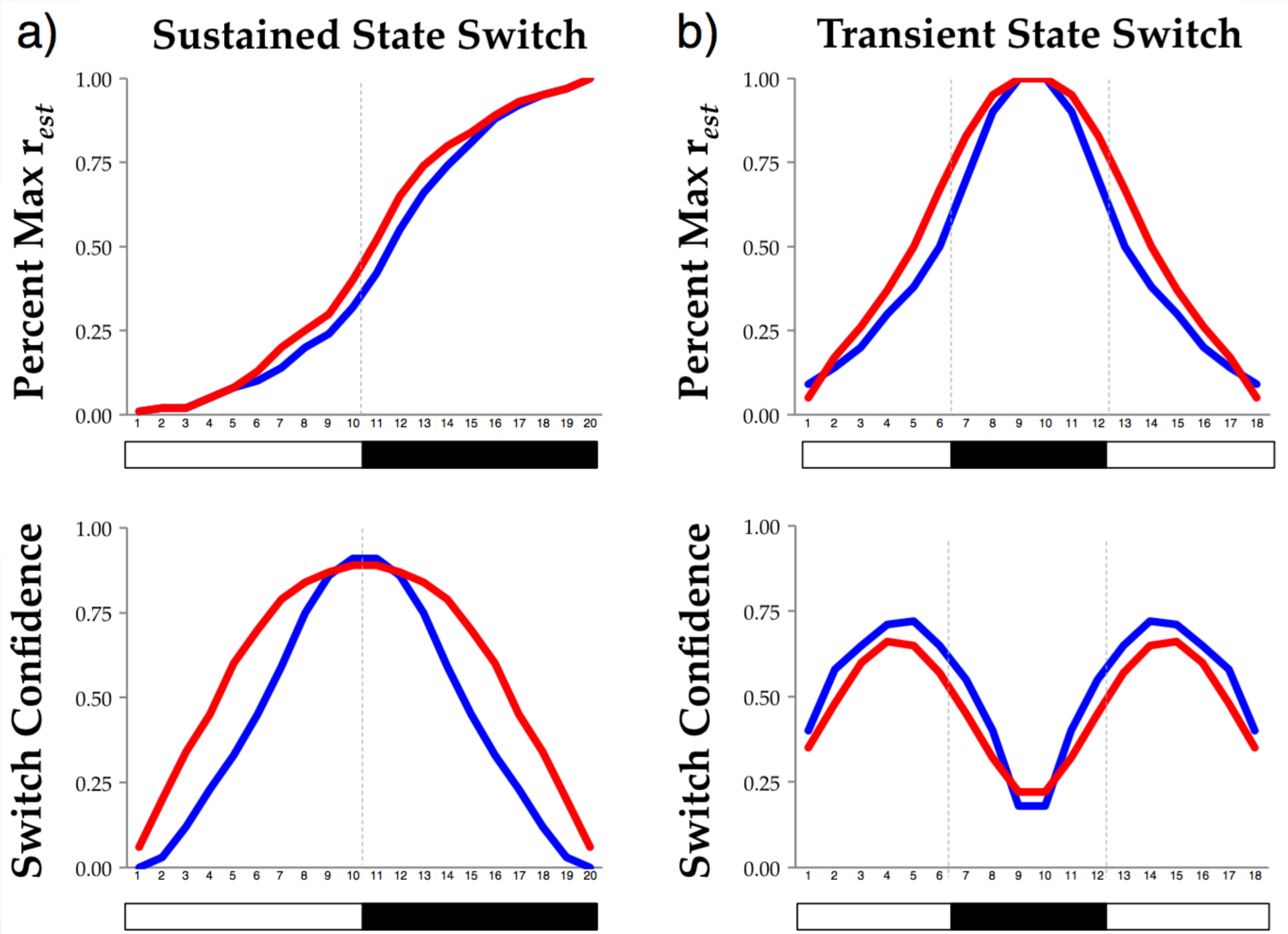
(plus regularized variations)

MTD: Multiplication of Temporal Derivatives



Shine et. al. (2015)

MTD vs. Pearson's



Shine et. al. (2015)

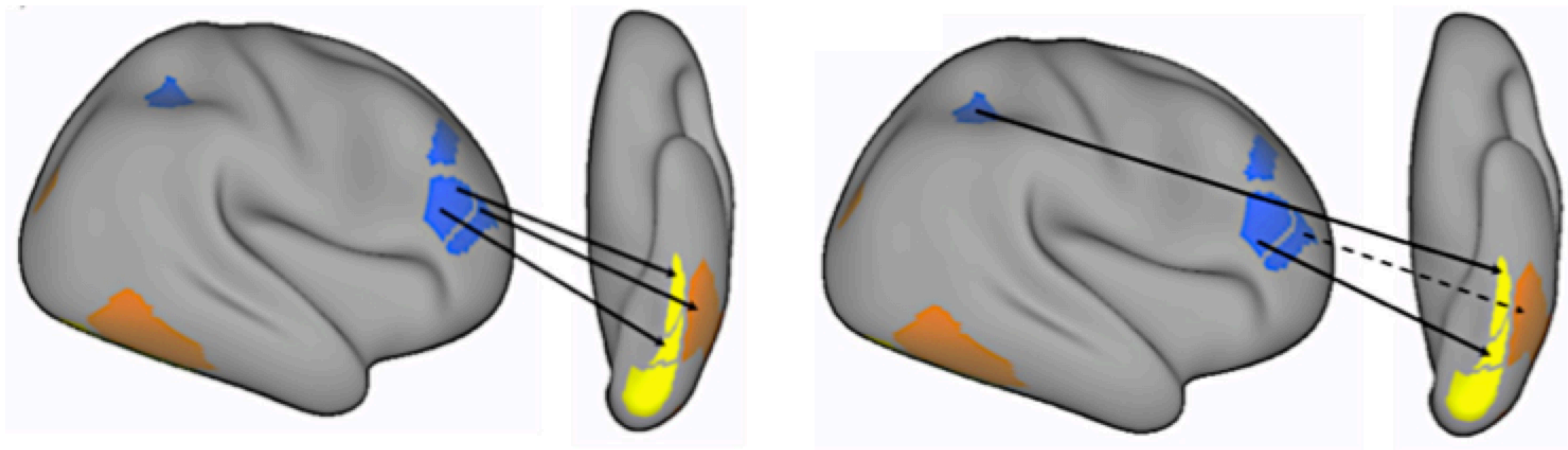
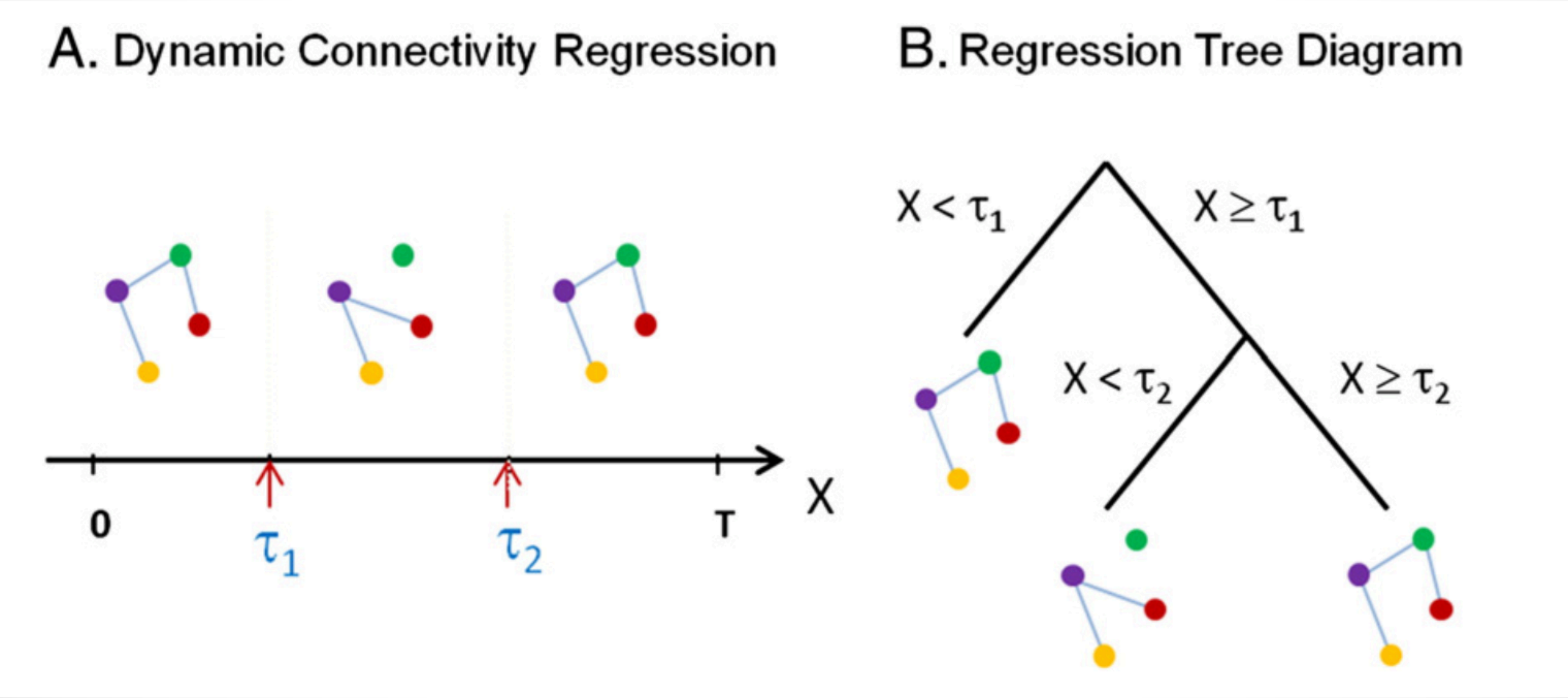


Figure 4 Increased task-based **functional connectivity between frontoparietal and ventral visual cortical parcels**: left – during 2-back blocks compared to 0-back blocks; right – during face vs place identification ($p < 0.001$; FDR 0.05).

- 40 subjects from the HCP, visual working memory
- 2-back vs. 0-back & Faces/Places/Tools/Body Parts
- MAC using Gordon ROI's

Shine et. al. (2015)

Change-Point Detection



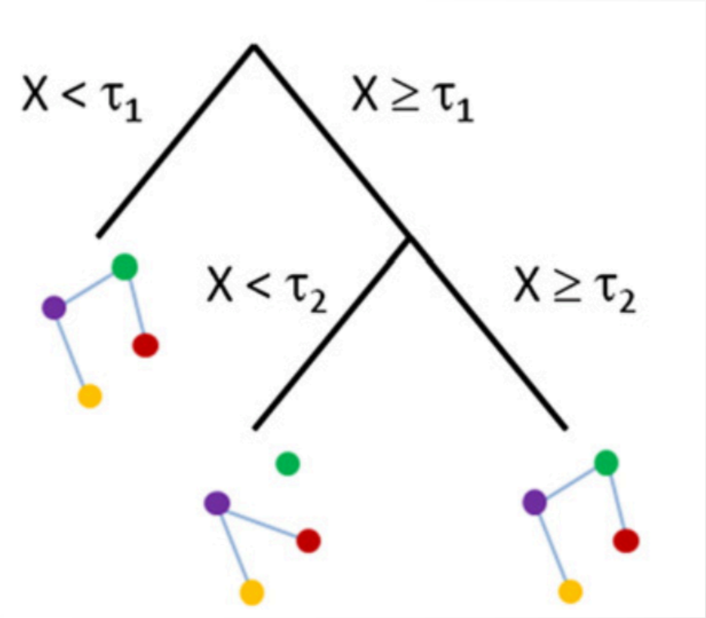
Cribben et. al. (2012)

Main Steps of DCR

- Select a statistic for connectivity within each window e.g. sparse precision
- Select a criterion for splitting the time series which balanced model fit vs. complexity e.g. BIC

Algorithm:

- (Recursively) at each leaf:
  - At each time point "t" within block
  - Estimate model with/without the split @ "t"
  - Compute best split "t*" within the block
  - Split the time series if it improves criterion

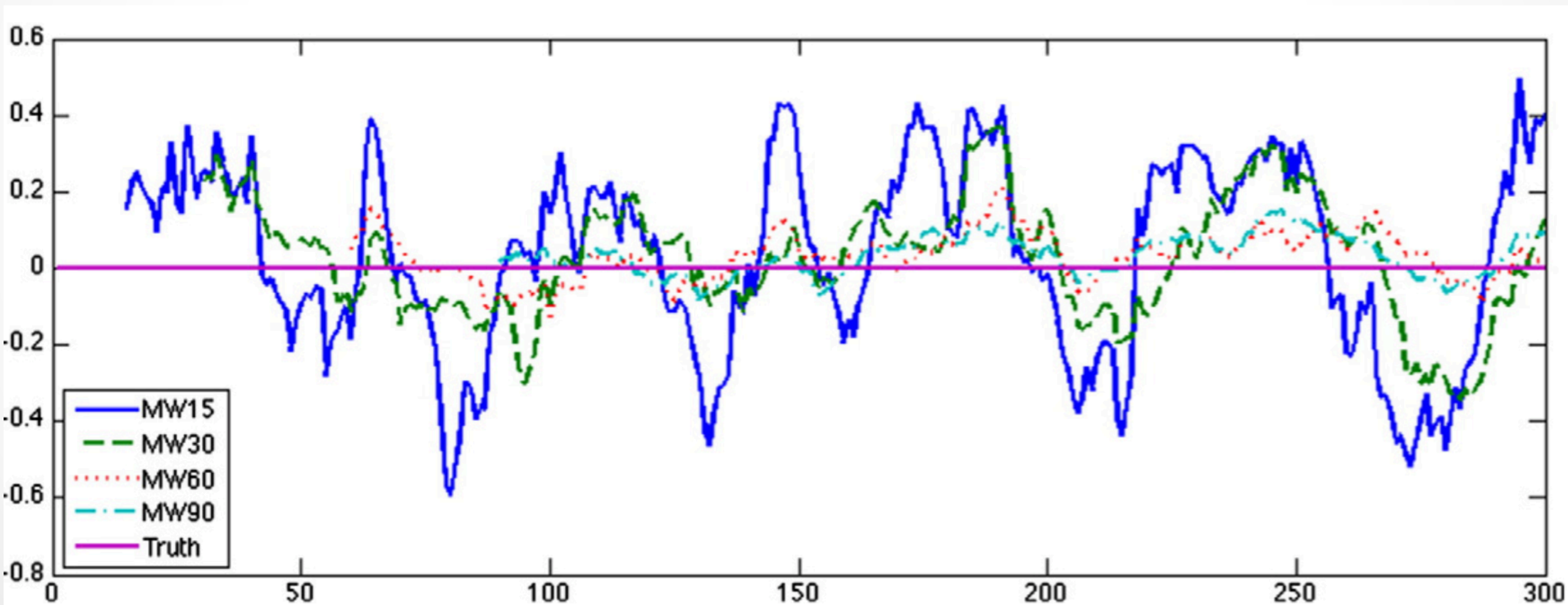


Pros of Non-Parametric Temporal Model

- No need to hypothesize model for temporal variation
- Easy to plug-in new kinds of connectivity estimators i.e. (sparse) precision, mutual information, multiplication of temporal derivatives
- Convenient for quick prototyping

Cons of Non-Parametric Temporal Model

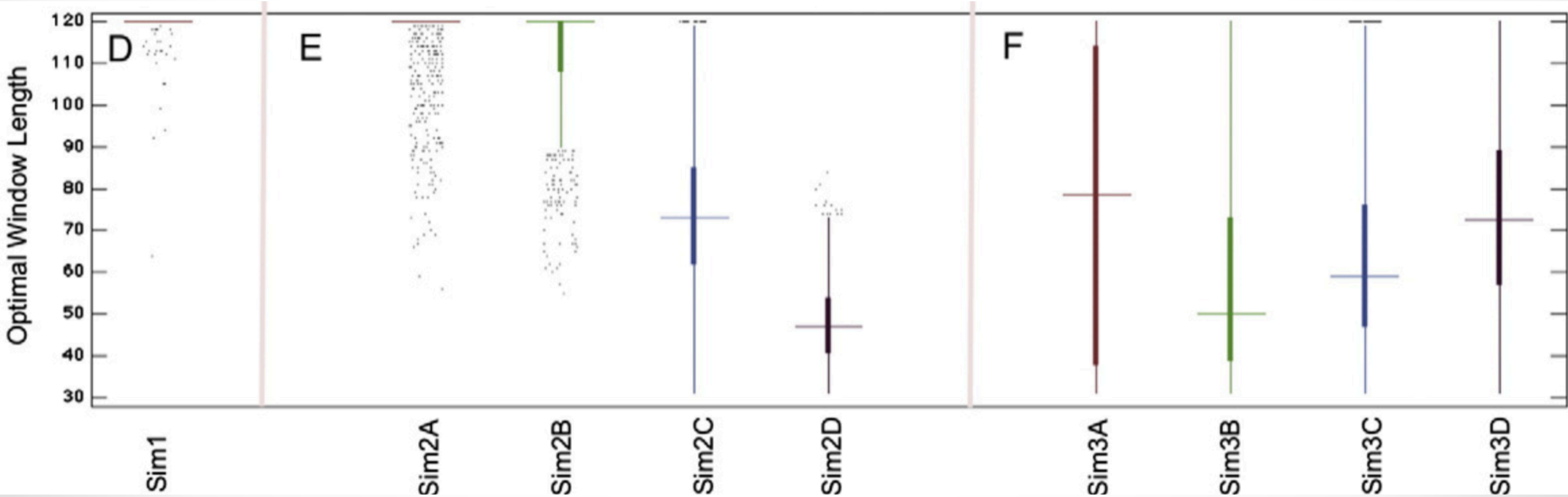
- Very limited data within each window, can lead to false positives



Lindquist et. al. (2014)

Cons of Non-Parametric Temporal Model

- May be difficult to scale e.g. DCR requires an exponential number of model evaluations wrt. length of the sample in the worst case
- Often sensitive to hyper-parameters



Lindquist et. al. (2014)

Outline

- ~~Introduction~~
- ~~Non-parametric temporal evolution~~
- **Parametric temporal evolution**
- Summary measures
- Inference
- Summary

Part 2

Parametric temporal variation

Univariate GARCH

- Popular for modeling financial time series
- Variance evolves following an ARMA-type model

$$y_t = \sigma_t \epsilon_t$$

$$\sigma_t^2 = \omega + \alpha y_{t-1}^2 + \beta \sigma_{t-1}^2 \qquad \text{GARCH (1,1)}$$

$$\sigma_t^2 = \omega + \sum_{i=1}^{p} \alpha_i y_{t-i}^2 + \sum_{j=1}^{q} \beta_j \sigma_{t-j}^2 \qquad \text{GARCH (p,q)}$$

Dynamic Conditional Correlation (DCC)

$$\sigma_{i,t}^2 = \omega_i + \alpha_i y_{i,t-1}^2 + \beta_i \sigma_{i,t-1}^2 \text{ for } i = 1,2$$

$$\mathbf{D}_t = diag\left\{\sigma_{1,t}, \sigma_{2,t}\right\}$$

Univariate GARCH

$$\epsilon_t = \mathbf{D}_t^{-1}\mathbf{e}_t$$

$$\mathbf{Q}_t = (1-\theta_1-\theta_2)\overline{\mathbf{Q}} + \theta_1 \epsilon_{t-1}\epsilon_{t-1}' + \theta_2 \mathbf{Q}_{t-1}$$

$$\mathbf{R}_t = diag\{\mathbf{Q}_t\}^{-1/2}\mathbf{Q}_t diag\{\mathbf{Q}_t\}^{-1/2}$$

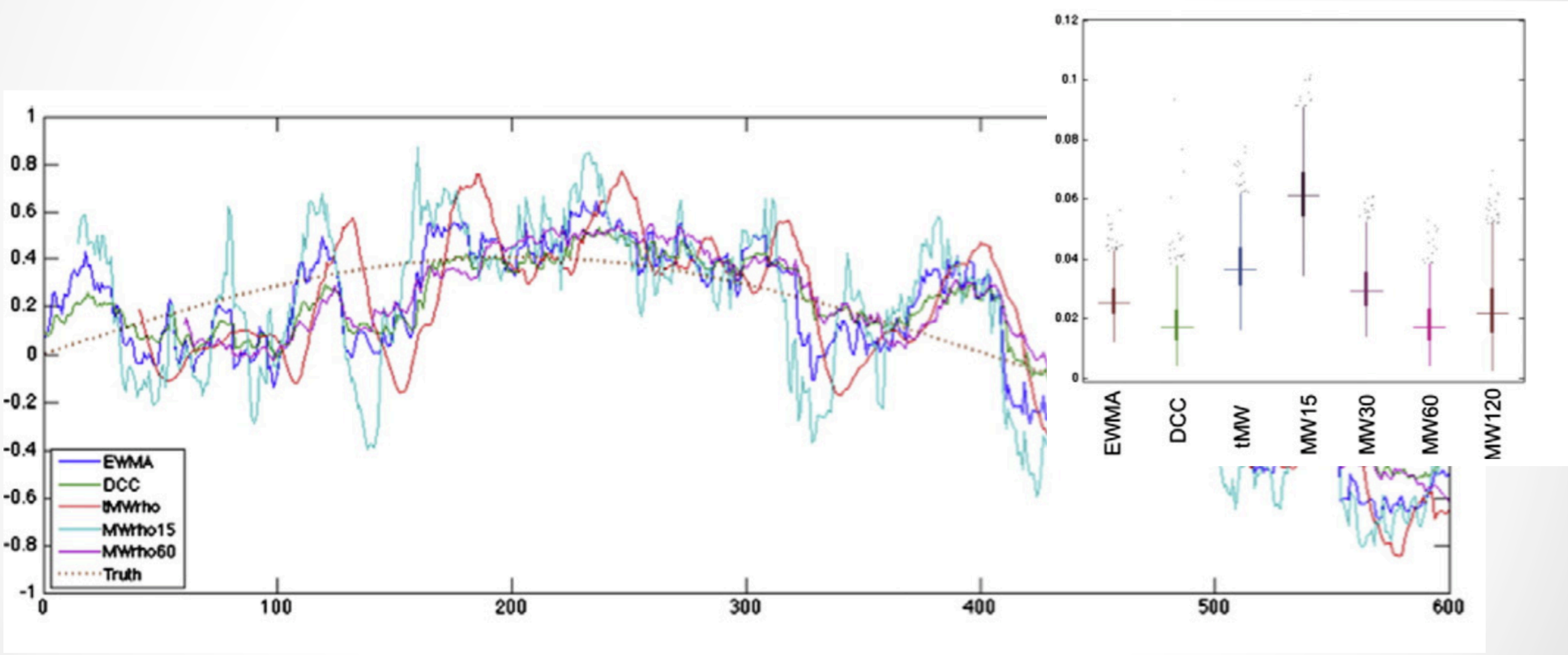
Cross-correlation

$$\Sigma_t = \mathbf{D}_t \mathbf{R}_t \mathbf{D}_t.$$

Combined covariance

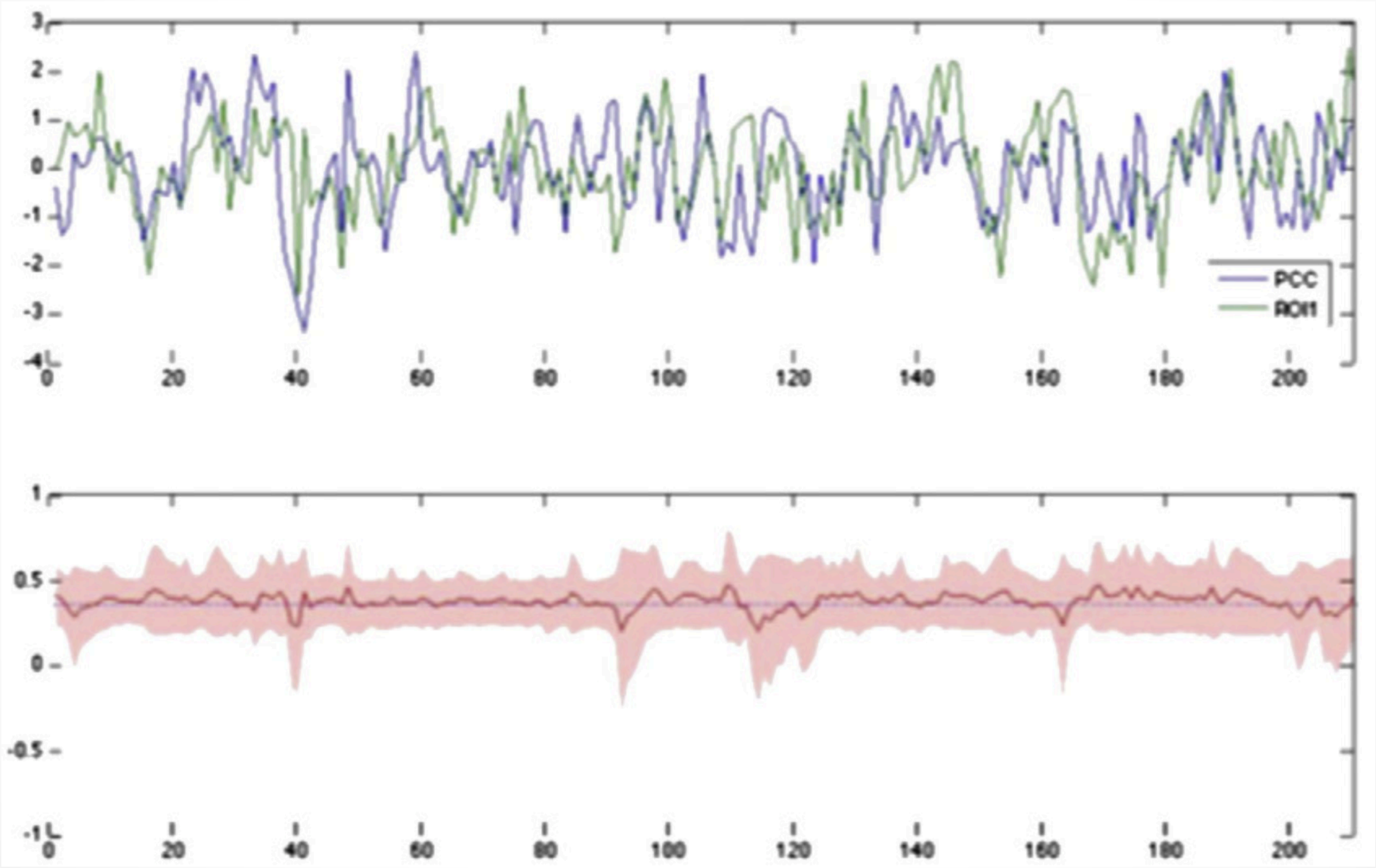
Fast+Efficient ML estimation

Sinusoidal Signal



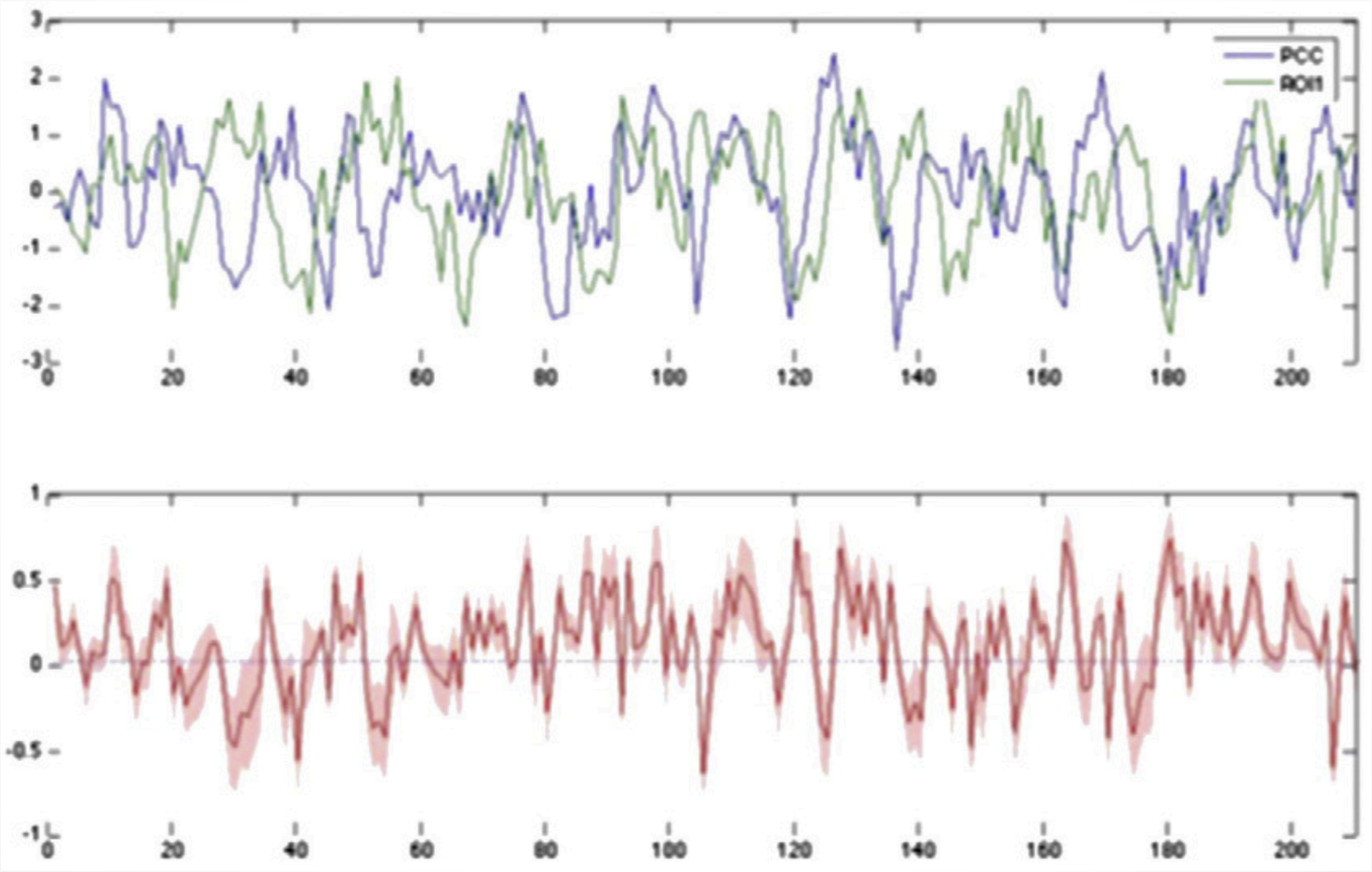
Lindquist et. al. (2014)

Application to Kirby 21 Dataset



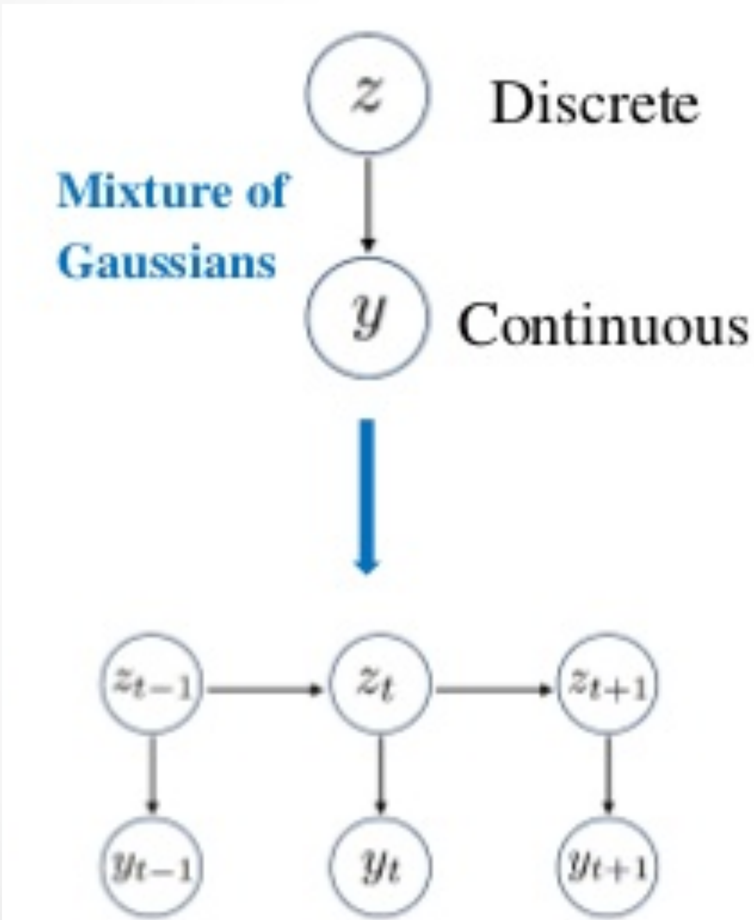
Lindquist et. al. (2014)

Application to Kirby 21 Dataset



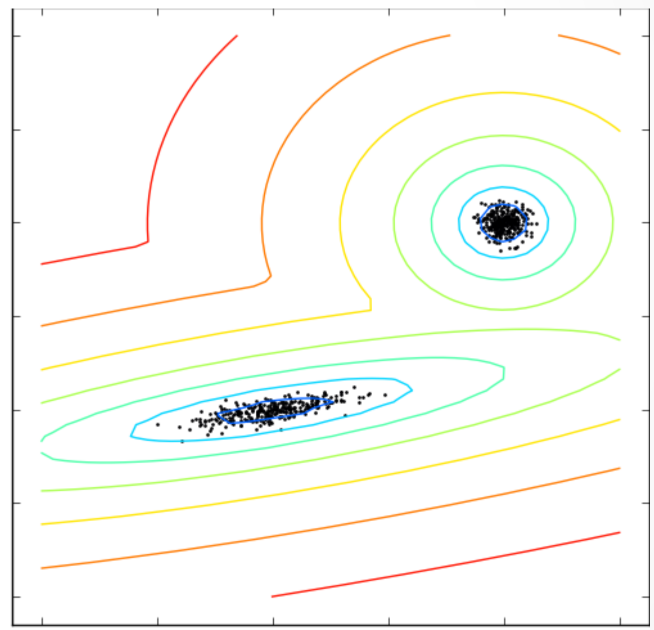
Lindquist et. al. (2014)

Discrete State Hidden Markov Model



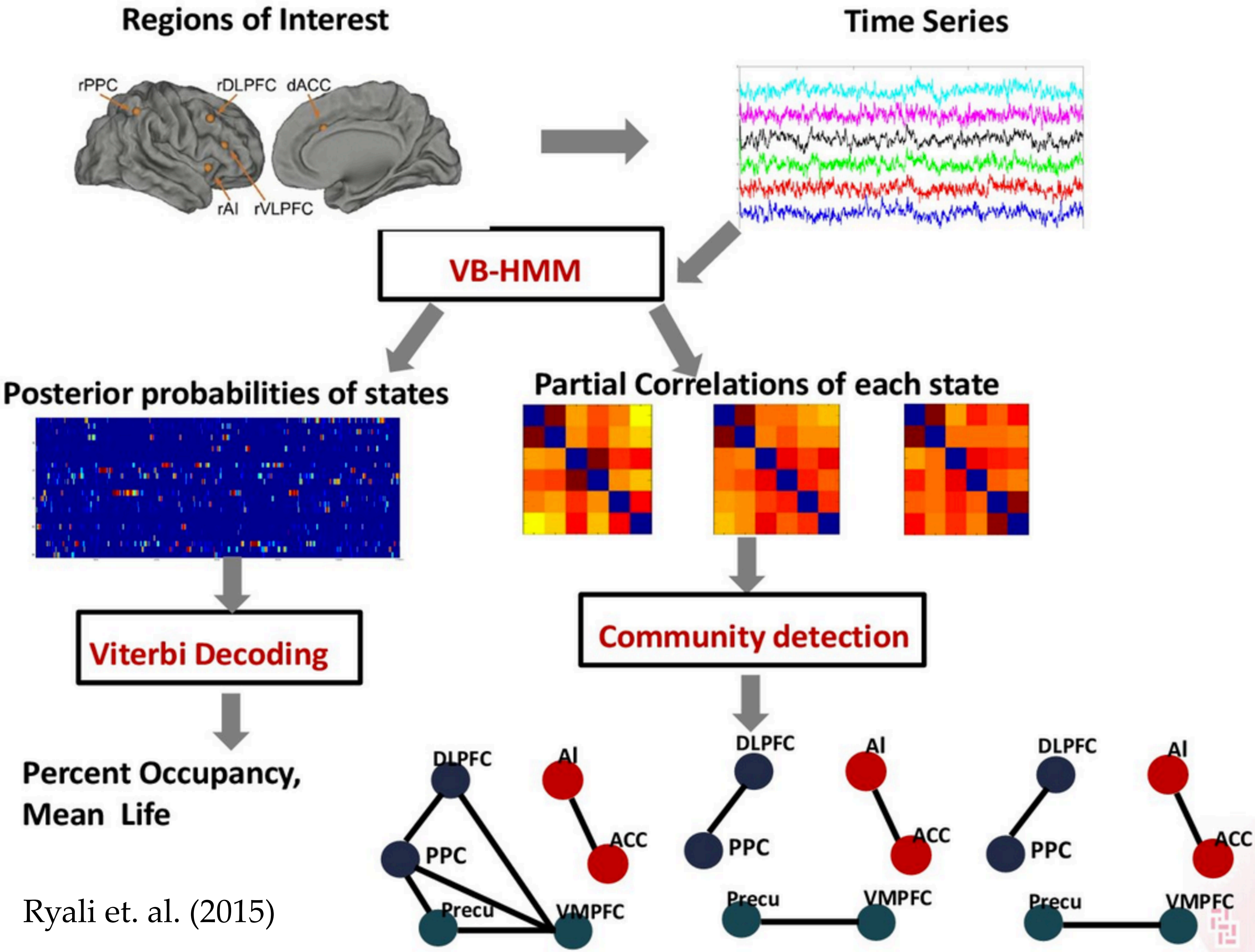
Liu (2014)

- Direct analogue to clustering



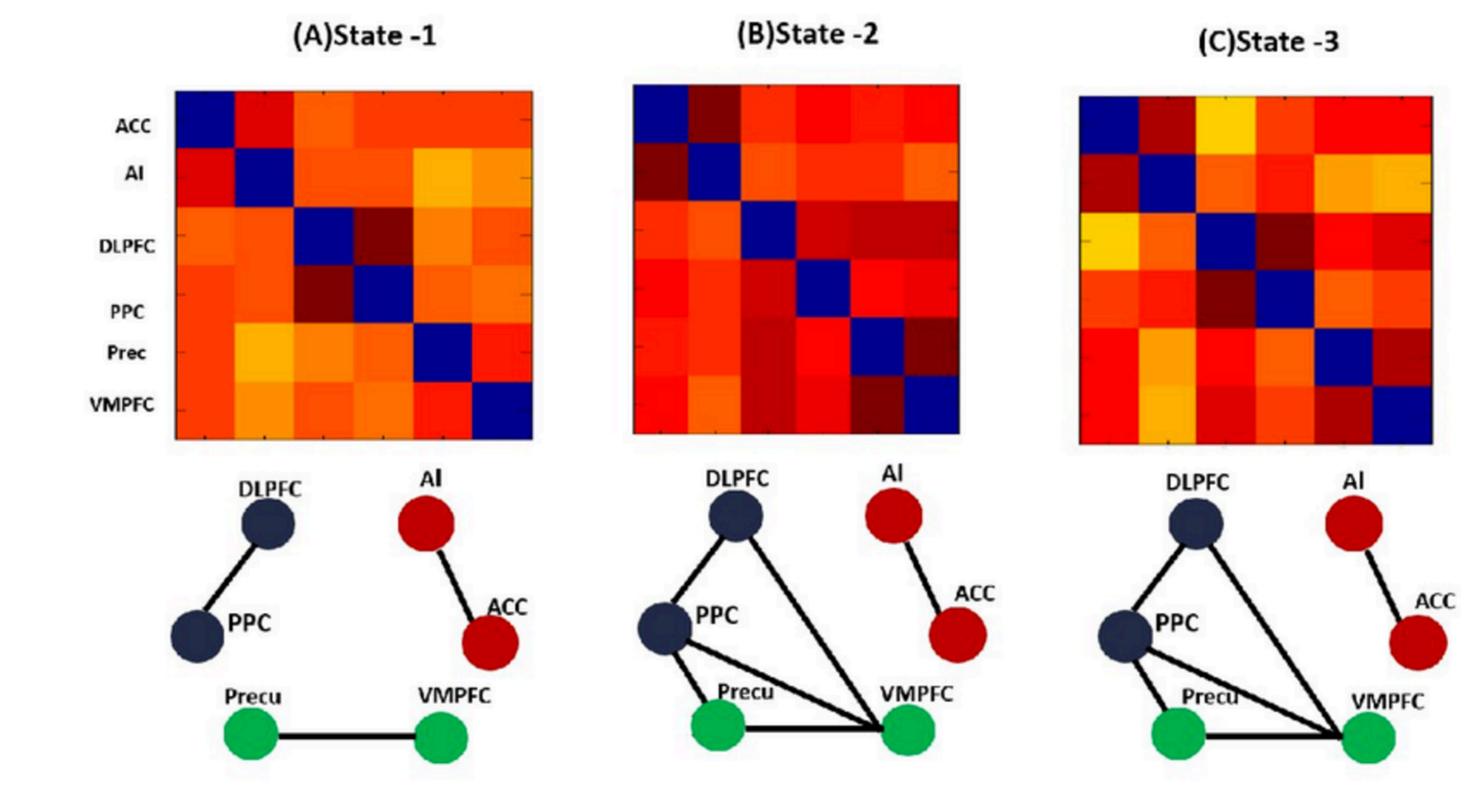
$$z_t \sim P(z_t | z_{t-1})$$

$$y_t \sim \mathcal{N}(\mu_{z_t}, \Sigma_{z_t})$$

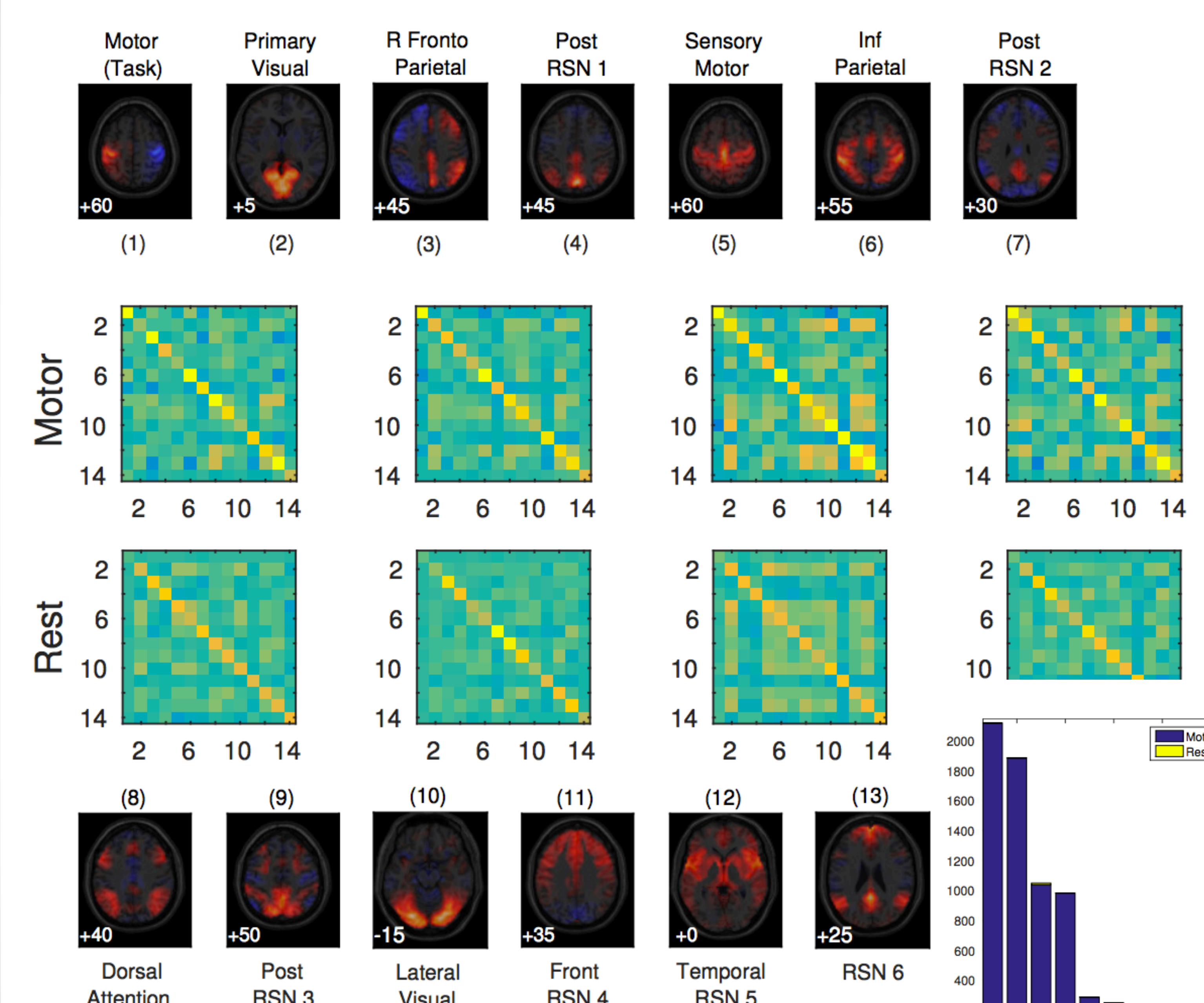


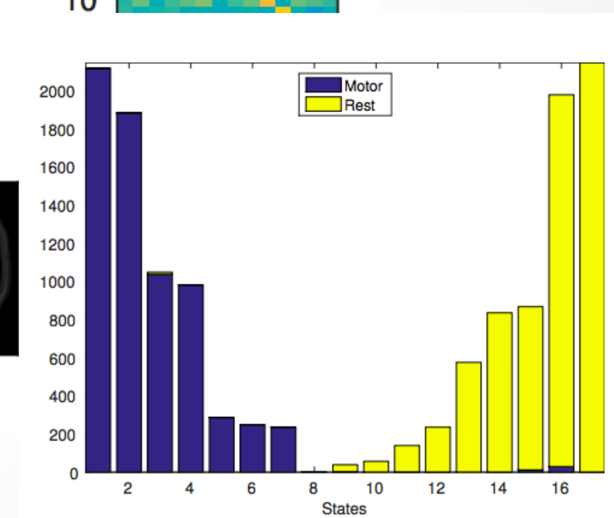
Ryali et. al. (2015)

Estimated Network States



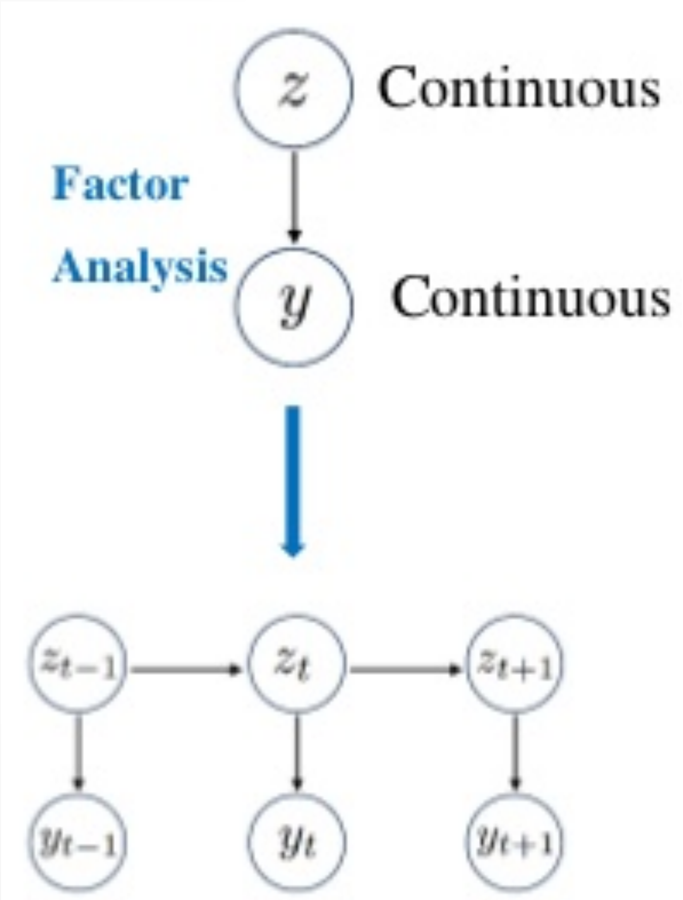
Ryali et. al. (2015)





- Nielsen et. al. (2016)

Continuous State Hidden Markov Model



Liu (2014)

- Direct analogue to factor analysis

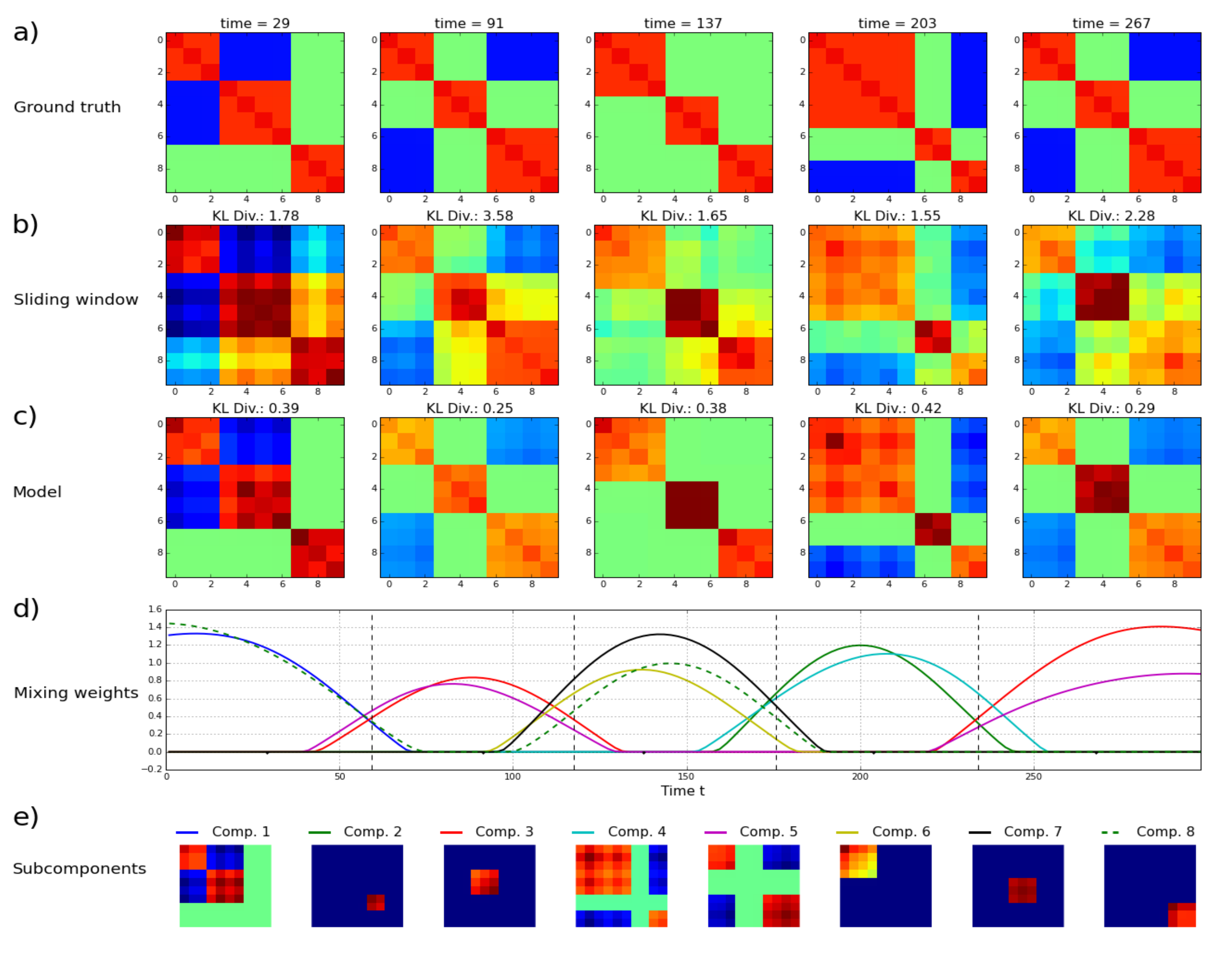
$$z_t \sim \mathcal{N}(0, S_t)$$

$$y_t \sim \mathcal{N}(V z_t, \sigma^2 I)$$

- Equivalent to evolving covariance model

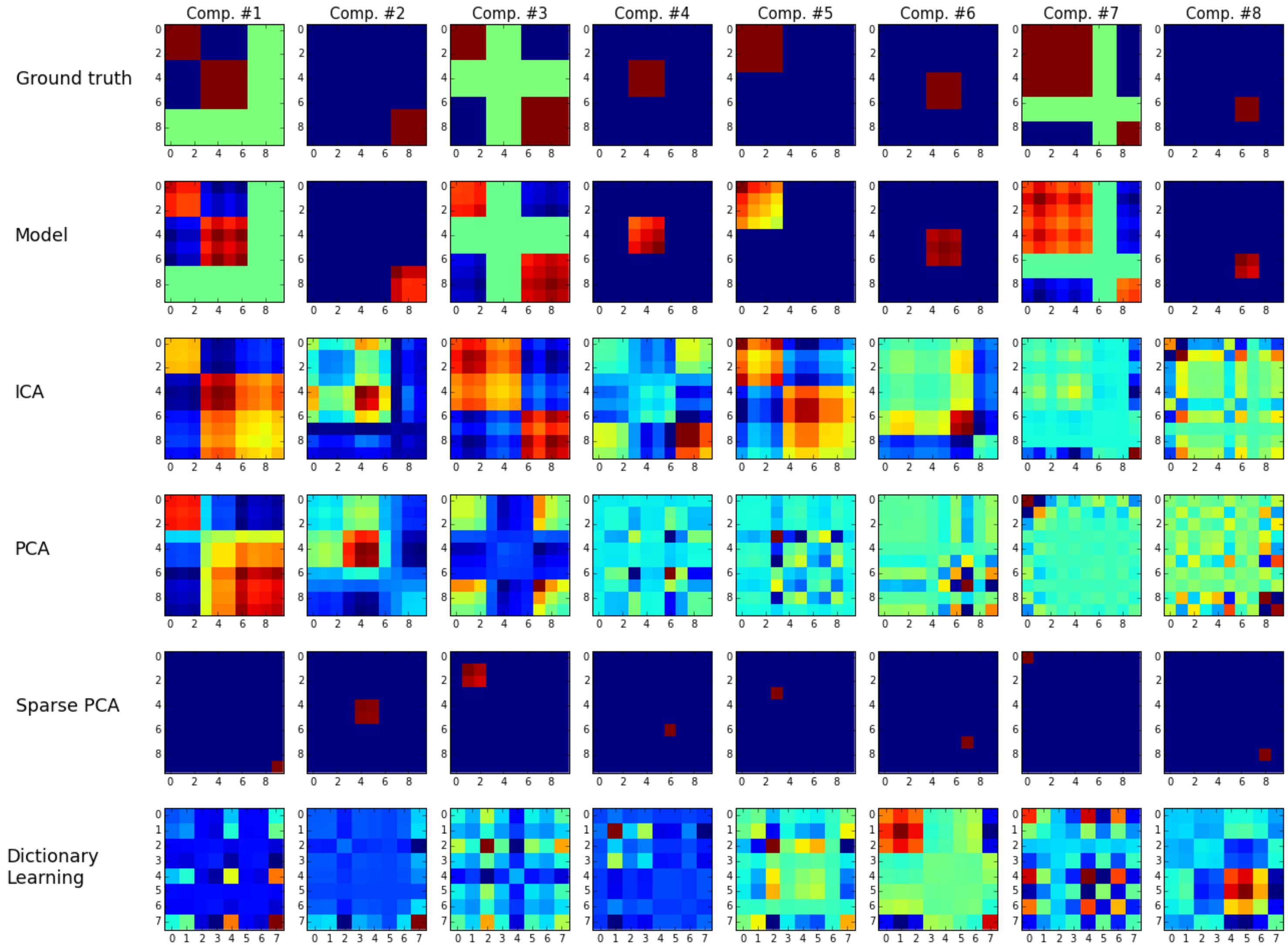
$$S_t \sim P(S_{t-1})$$

$$y_t \sim \mathcal{N}(0, V S_t V' + \sigma^2 I)$$



Andersen et. al. (2016)

Factor Model Visualization



Andersen et. al. (2016)

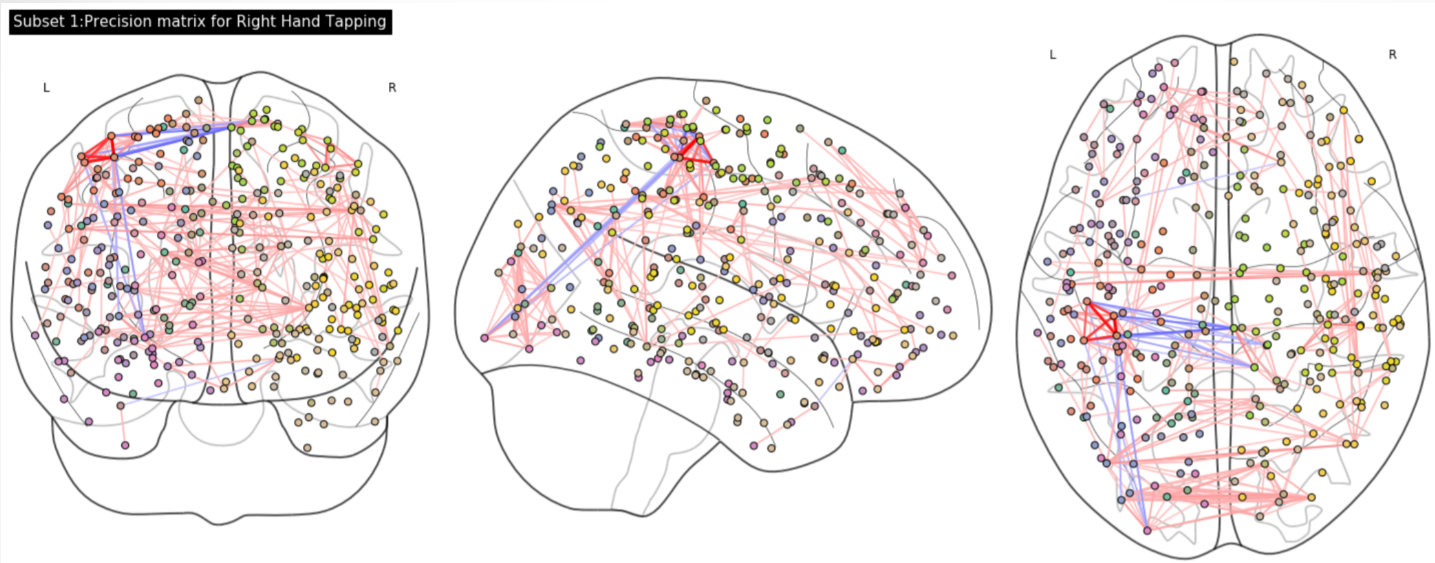
Classification Accuracy

- HCP data, Gordon 333 atlas, Motor task
- Task block + motion regressed out, model the residual
- Train on 5 subjects, test on held out subjects using log likelihood

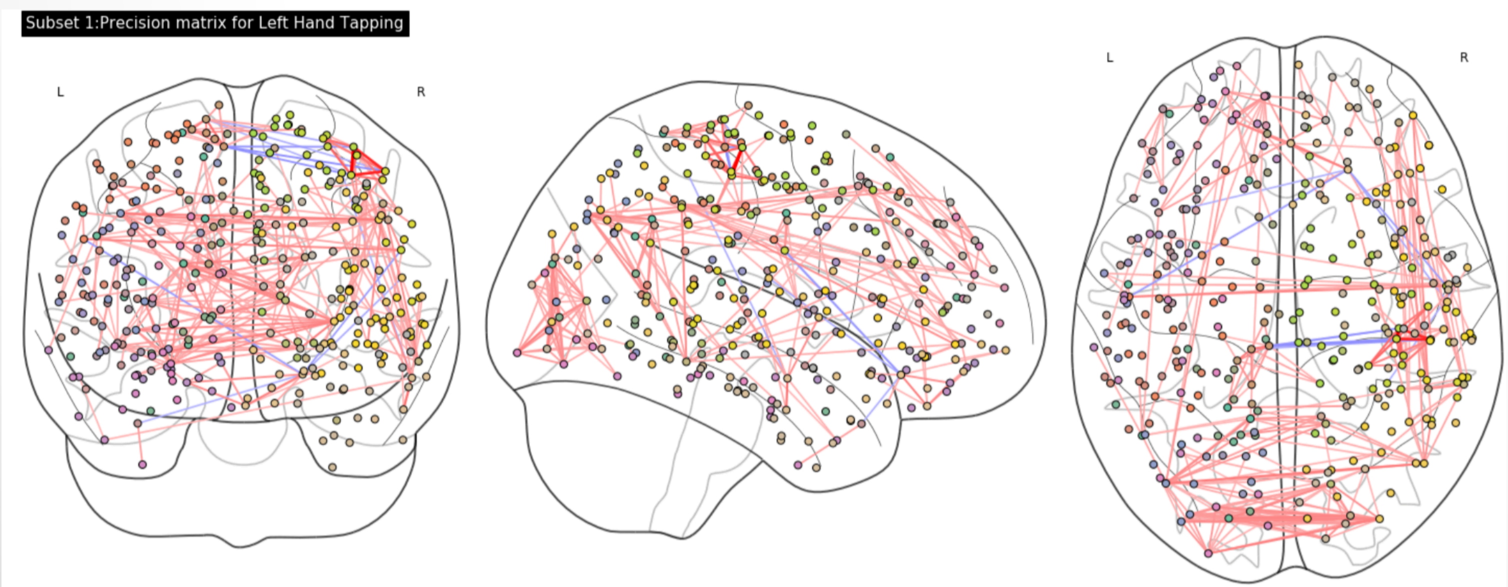
Task	Classification using model	Random guessing
Right Hand Tapping	0.784 (0.078)	0.167 (0.112)
Left Foot Tapping	0.523 (0.197)	0.169 (0.116)
Tongue Wagging	0.420 (0.136)	0.174 (0.121)
Right Foot Tapping	0.409 (0.208)	0.170 (0.112)
Left Hand Tapping	0.761 (0.136)	0.168 (0.116)
Rest	0.352 (0.132)	0.161 (0.111)

Andersen et. al. (2016), In prep.

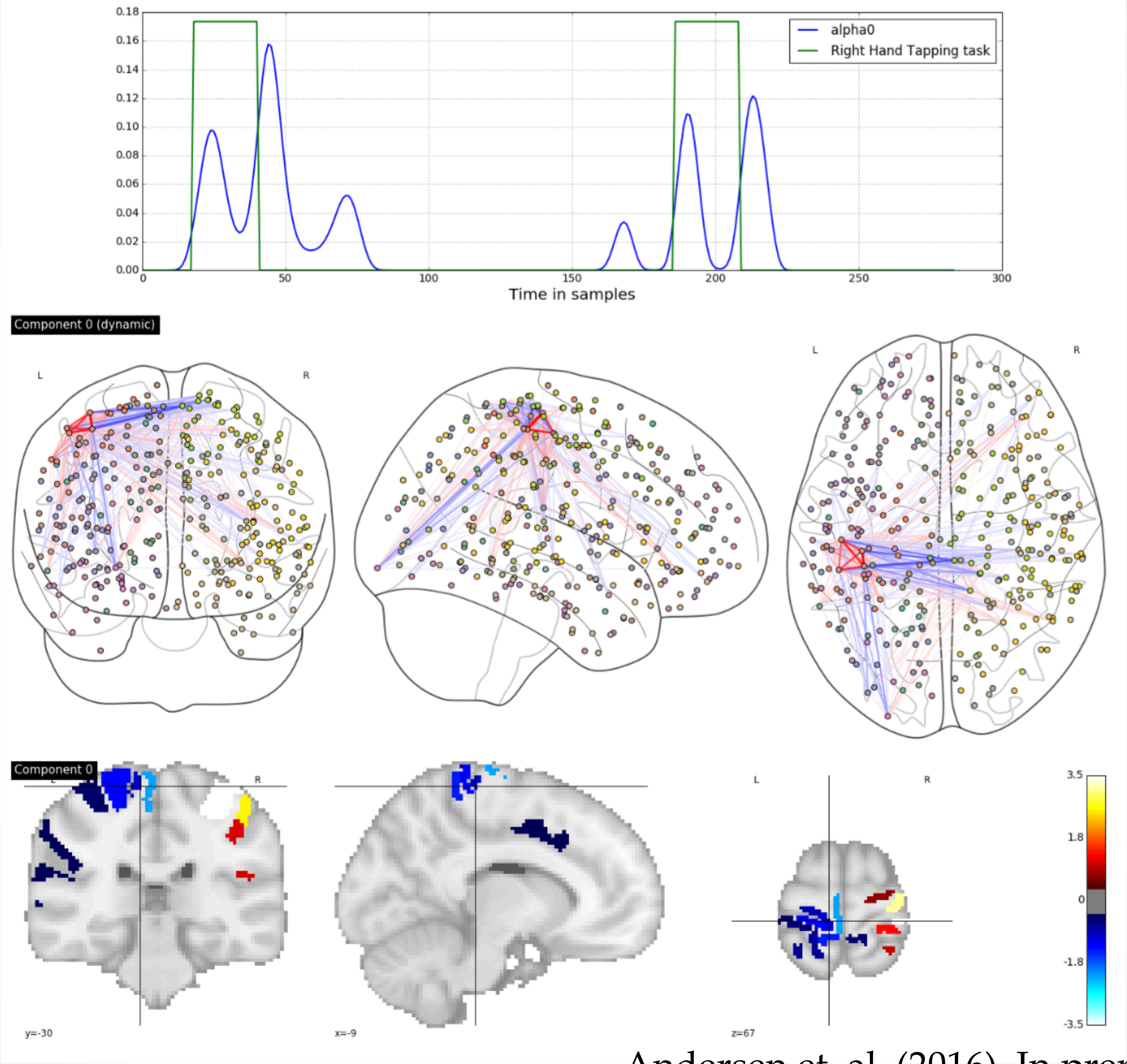
Andersen et. al. (2016), In prep.



Right hand



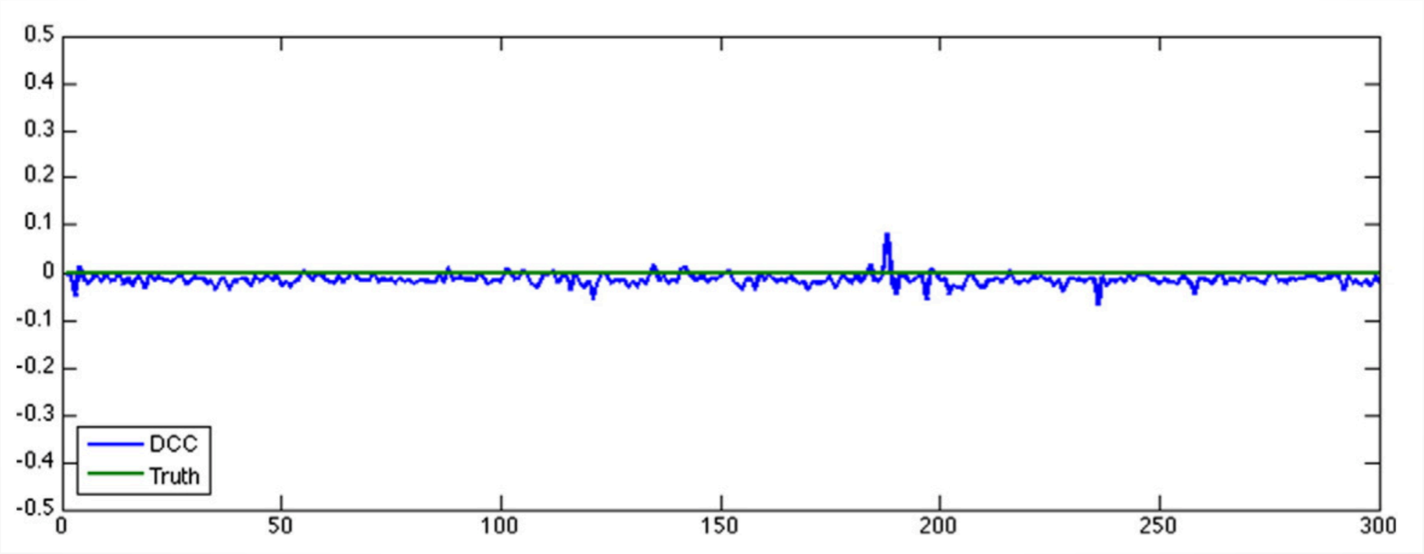
Left hand



Andersen et. al. (2016), In prep.

Pros of Parametric Temporal Model

- Very accurate when model structure is evident in the data
- Tends to be conservative when model structure is not a strong signal



Lindquist et. al. (2014)

Pros of Parametric Temporal Model

- Explicit about underlying assumptions
- Model summaries are often built-in (discrete HMM) e.g. graph states, temporal variation
- Estimation can be faster than non-parametric approaches for simple models
- Certain parametric models have built-in inference

Cons of Parametric Temporal Model

- Often requires expert knowledge to develop and fit the model e.g. variational inference, Viterbi decoding, …
- May be computationally expensive, particularly when using complicated models with many parameters
- As in all models, some risk of false negative when model does not match data

Ipython Notebook Example

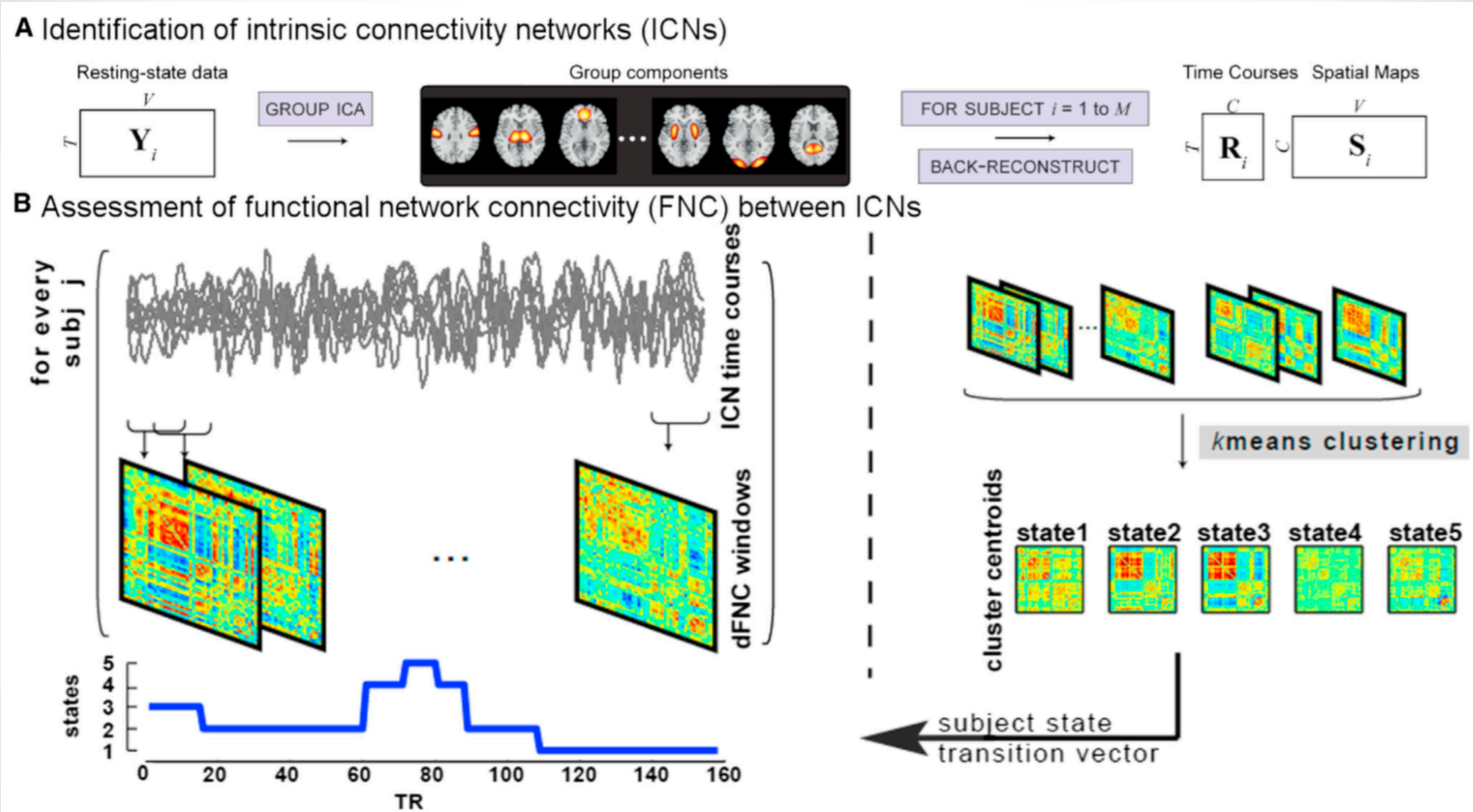
Comparing sliding window to HMM model fit

Outline

- ~~Introduction~~
- ~~Non-parametric temporal evolution~~
- ~~Parametric temporal evolution~~
- **Summary measures**
- Inference
- Summary

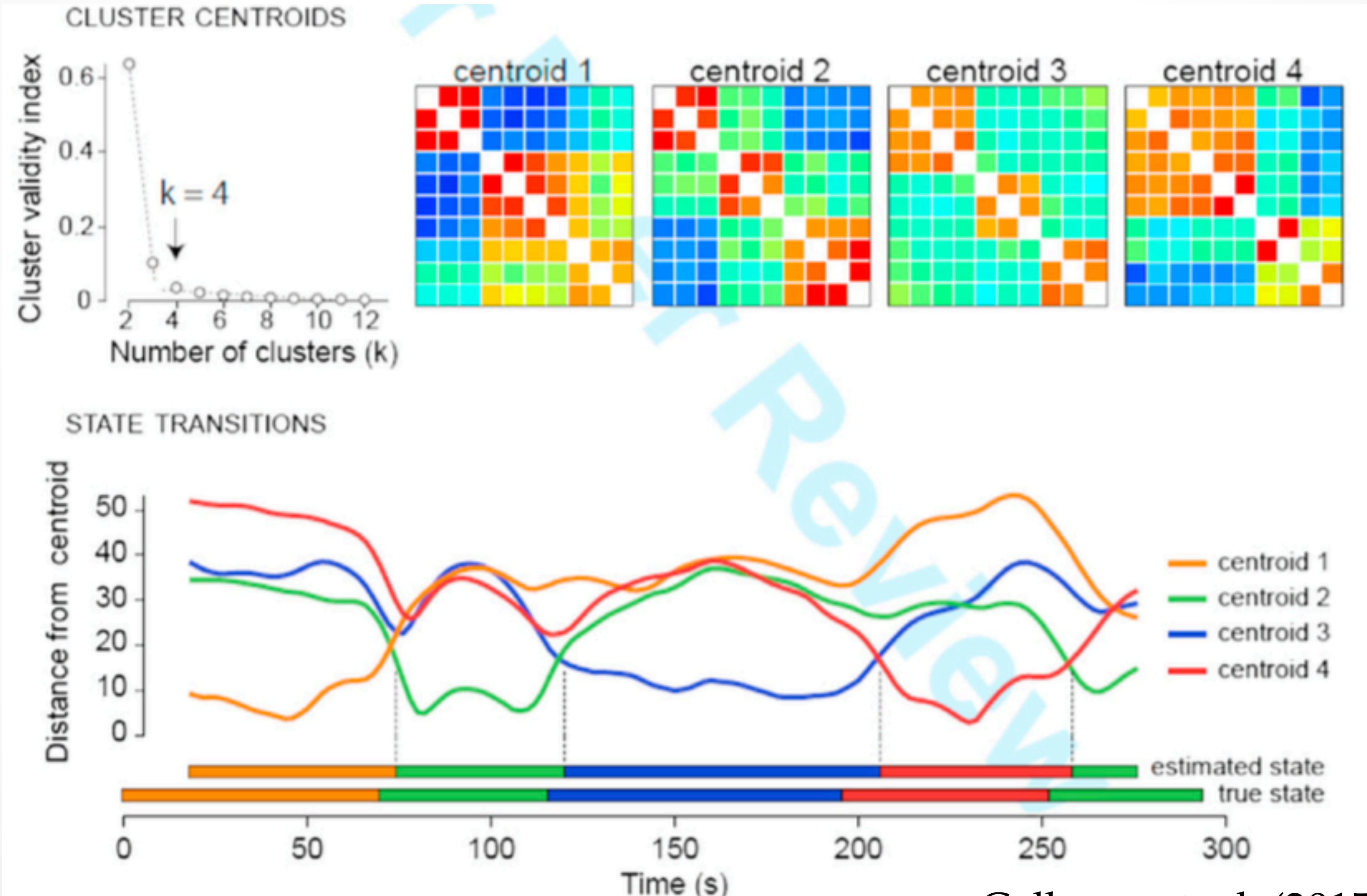
Part 3

Summary Measures



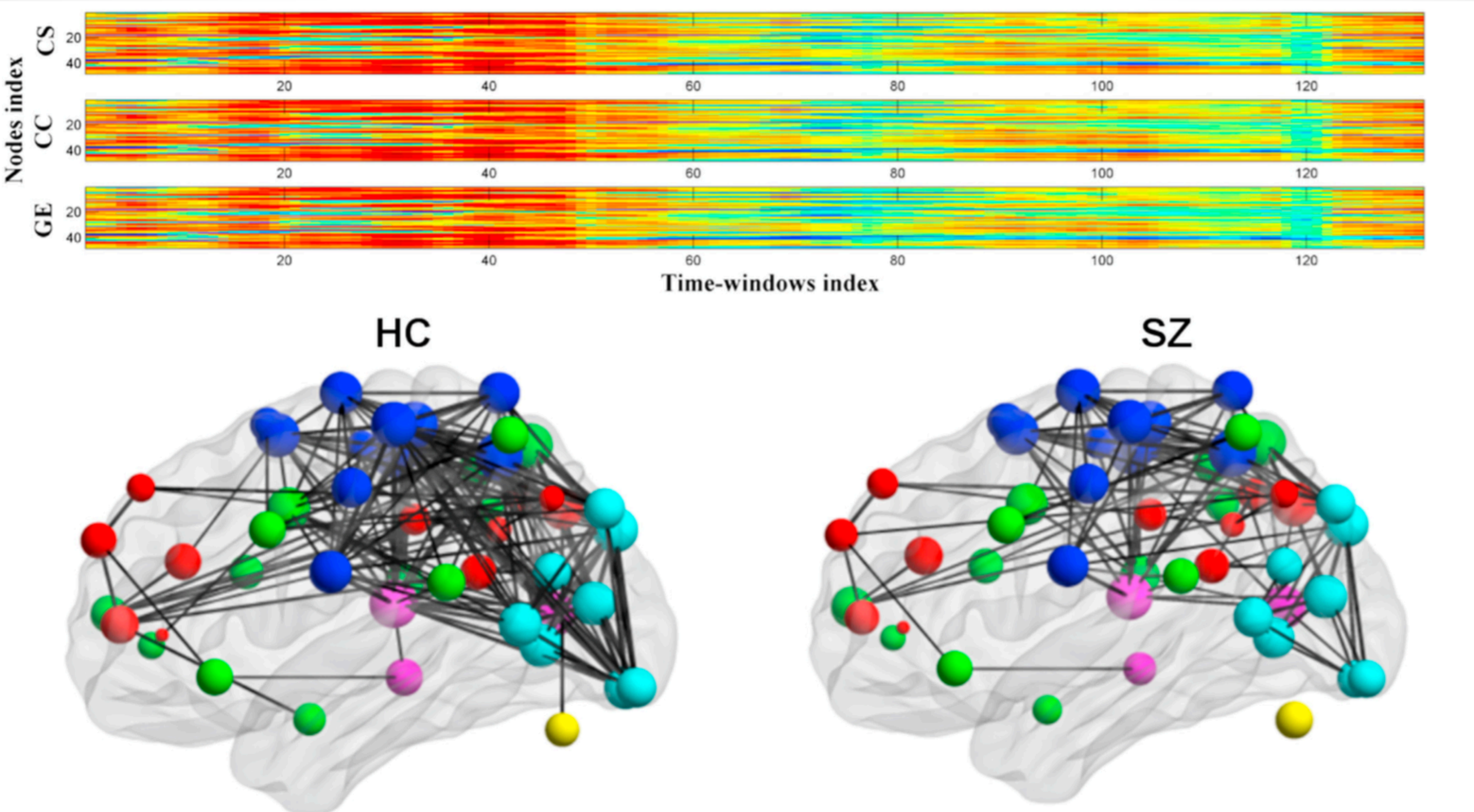
Calhoun et. al. (2015)

Cluster & Estimate States

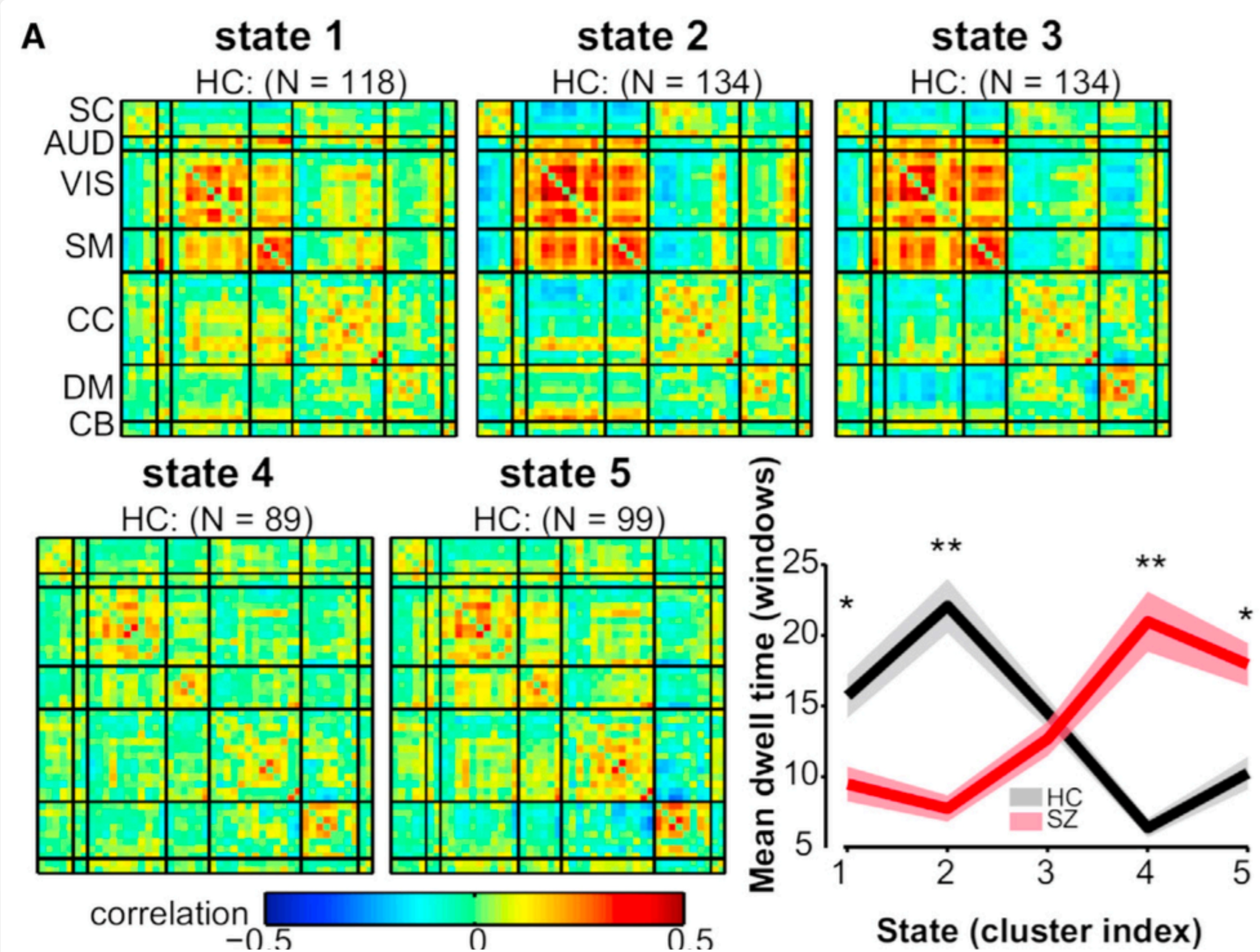


Calhoun et. al. (2015)

Model State Transitions



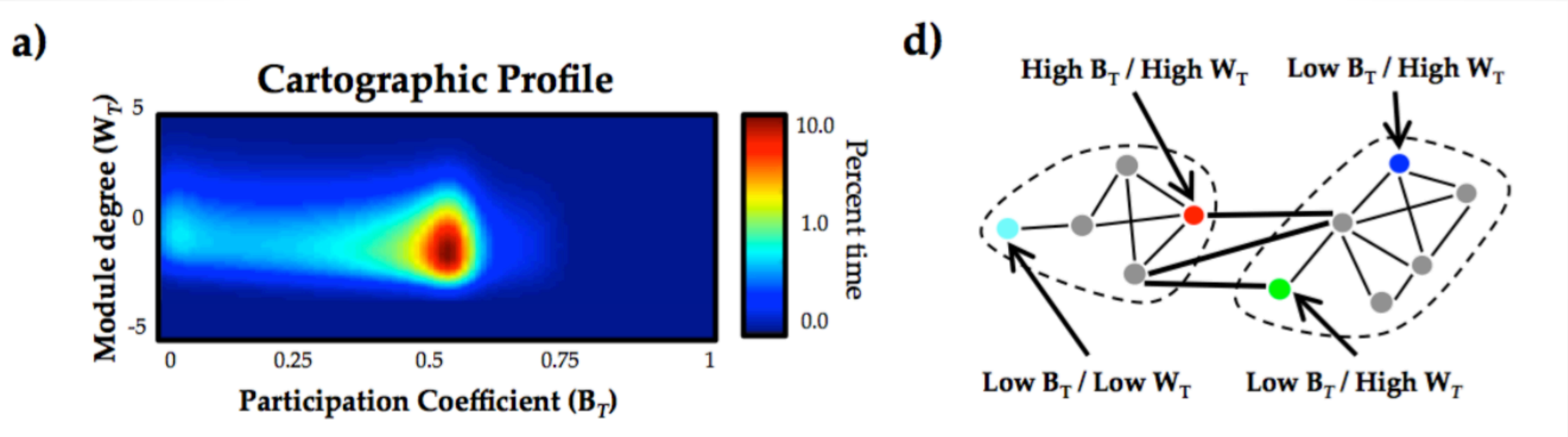
Calhoun et. al. (2015)



Dynamics of Schizophrenia vs. healthy controls
(Calhoun et. al., 2015)

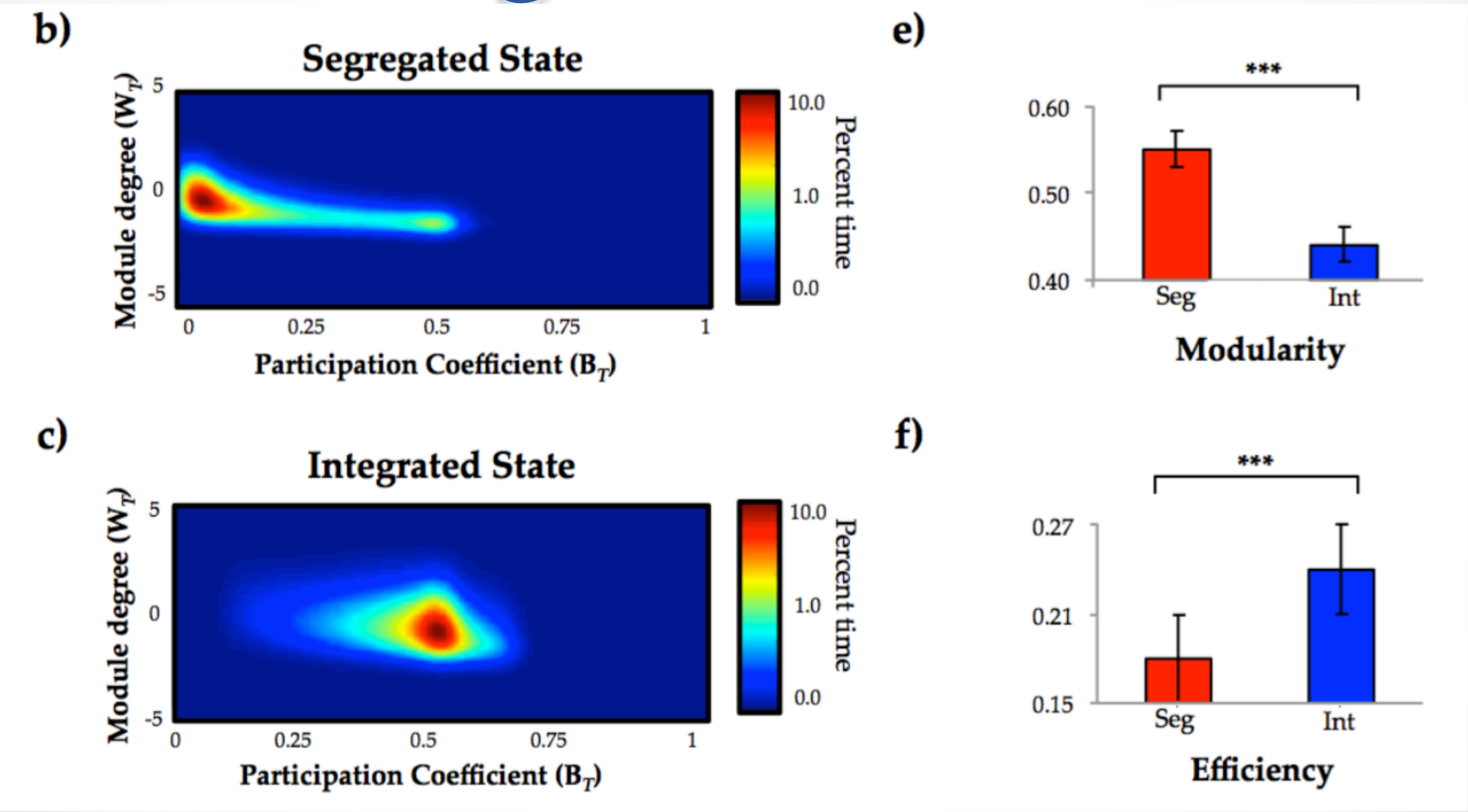
Cartographic Profiling

- Estimate modules (clusters) between voxels/regions at each time point
- Compute graph statistics e.g. module degree, participation coefficient



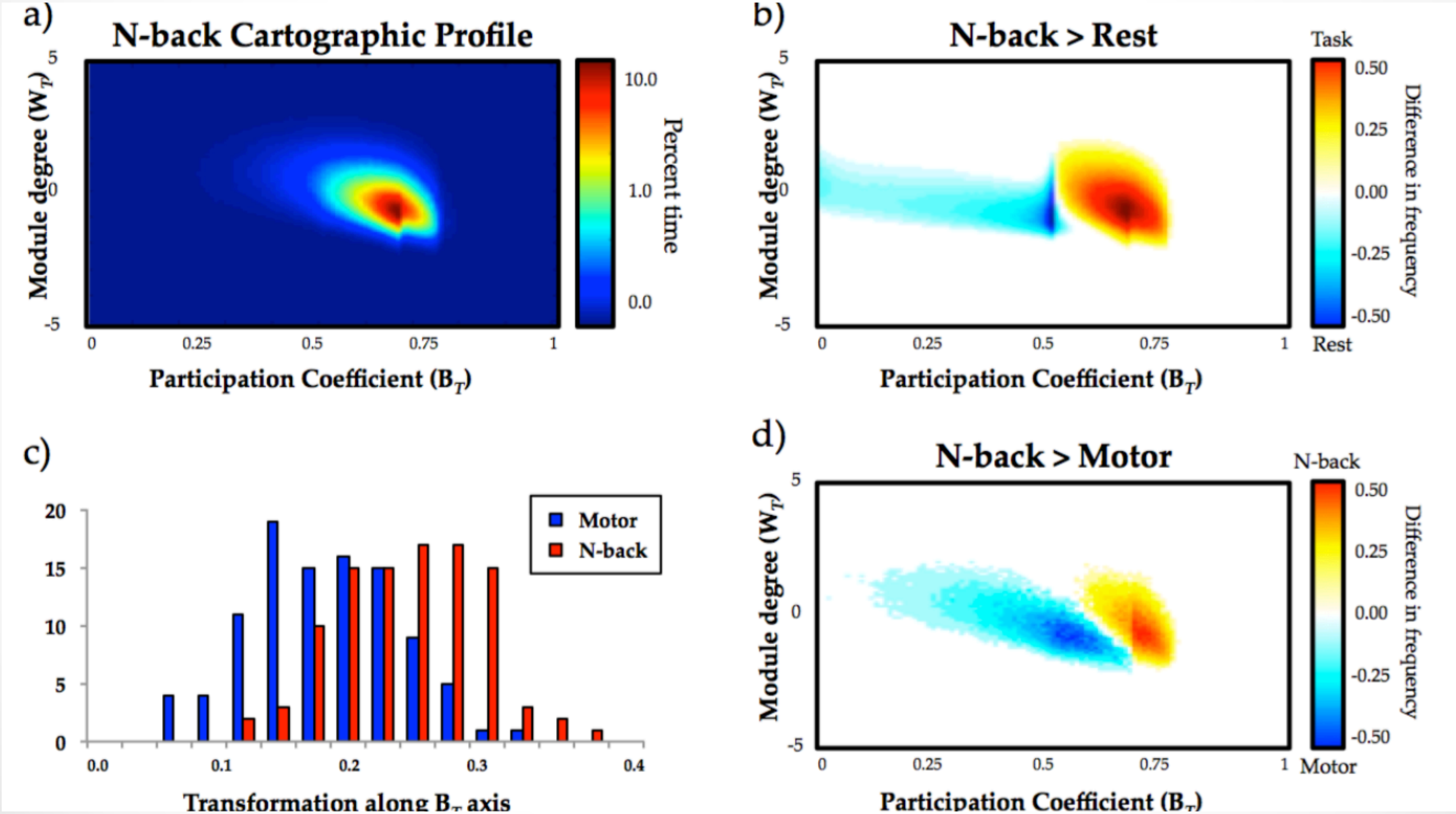
Shine et. al. (2016), Submitted

Distinct Segregated and Integrated States



Shine et. al. (2016), Submitted

Differences in Task vs. Rest



Summaries for Parametric Temporal Evolution

- Parametric models often have "natural" interpretations e.g. Gaussian HMM automatically estimates "states"
- However, can be difficult to synthesize interpretation for large models
- Suggest to combine both parametric and non-parametric summaries to fully explore the results

Outline

- ~~Introduction~~
- ~~Non-parametric temporal evolution~~
- ~~Parametric temporal evolution~~
- ~~Summary measures~~
- **Inference**
- Summary

Part 4

Inference

Asymptotic Tests

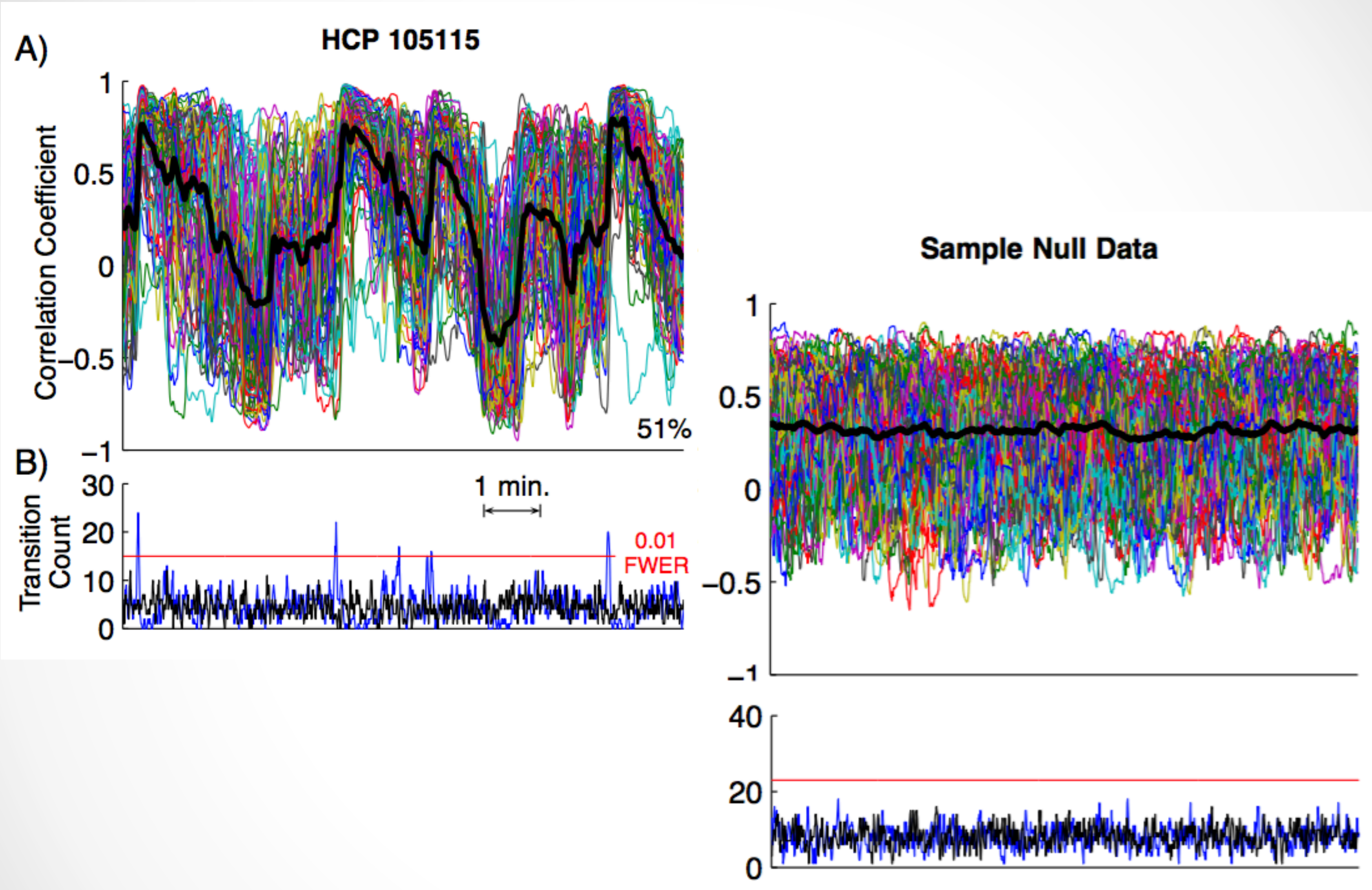
- Often interested in rejecting the null hypothesis that non-zero graph edges are due to chance
- Asymptotic tests are not exact, but typically perform well in simulation tests

- There is a test statistic for DCC that is asymptotically normal (Engle & Sheppard., 2001)
- There is a test statistic for sliding window kernel (sparse) precision estimation that is asymptotically normal, even for high dimensional data (Wang & Kolar, 2014, Junwei et. al., 2015)

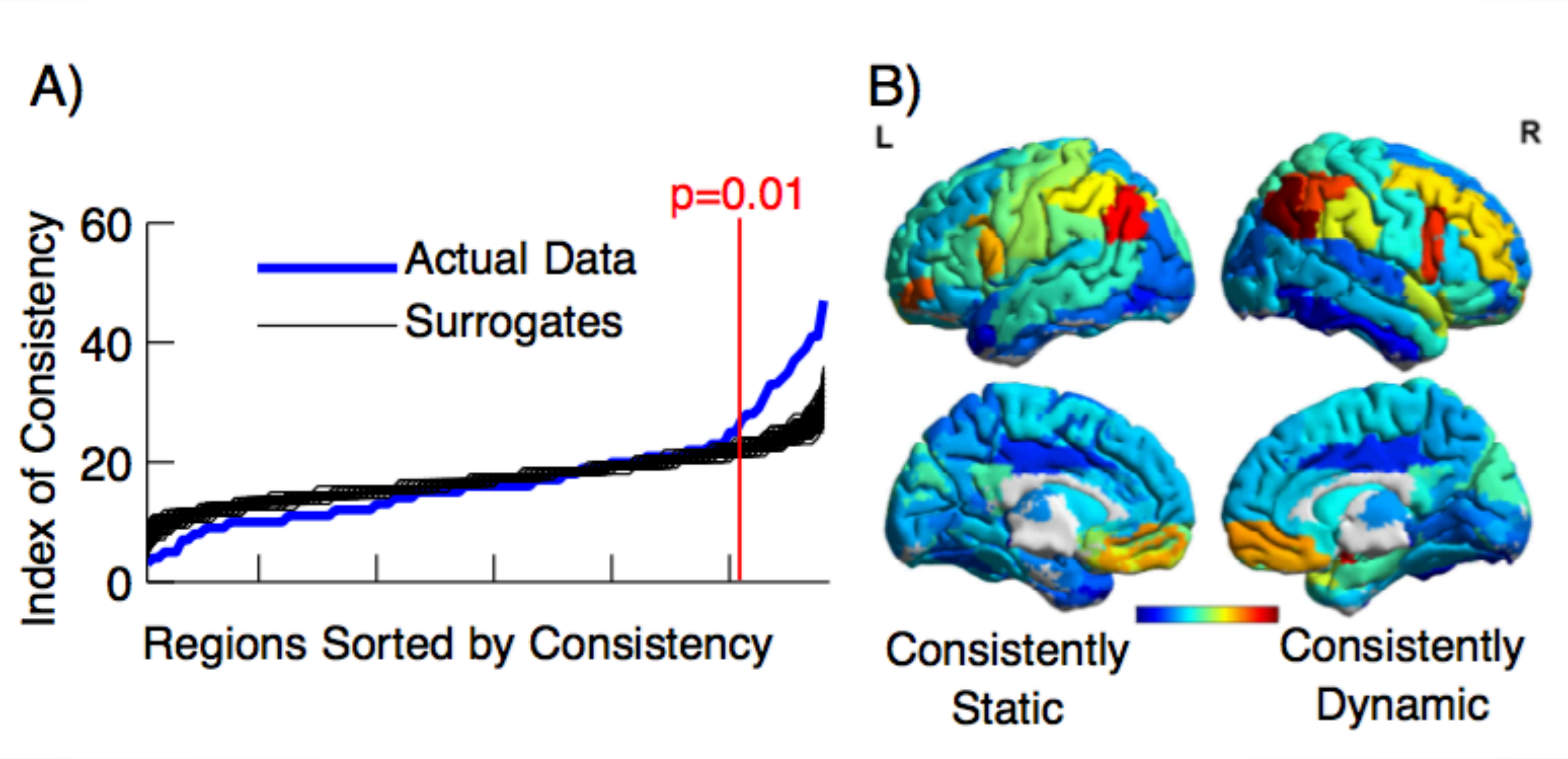
Non-parametric test

- Parametric tests may not exist for interesting statistics such as summary measures

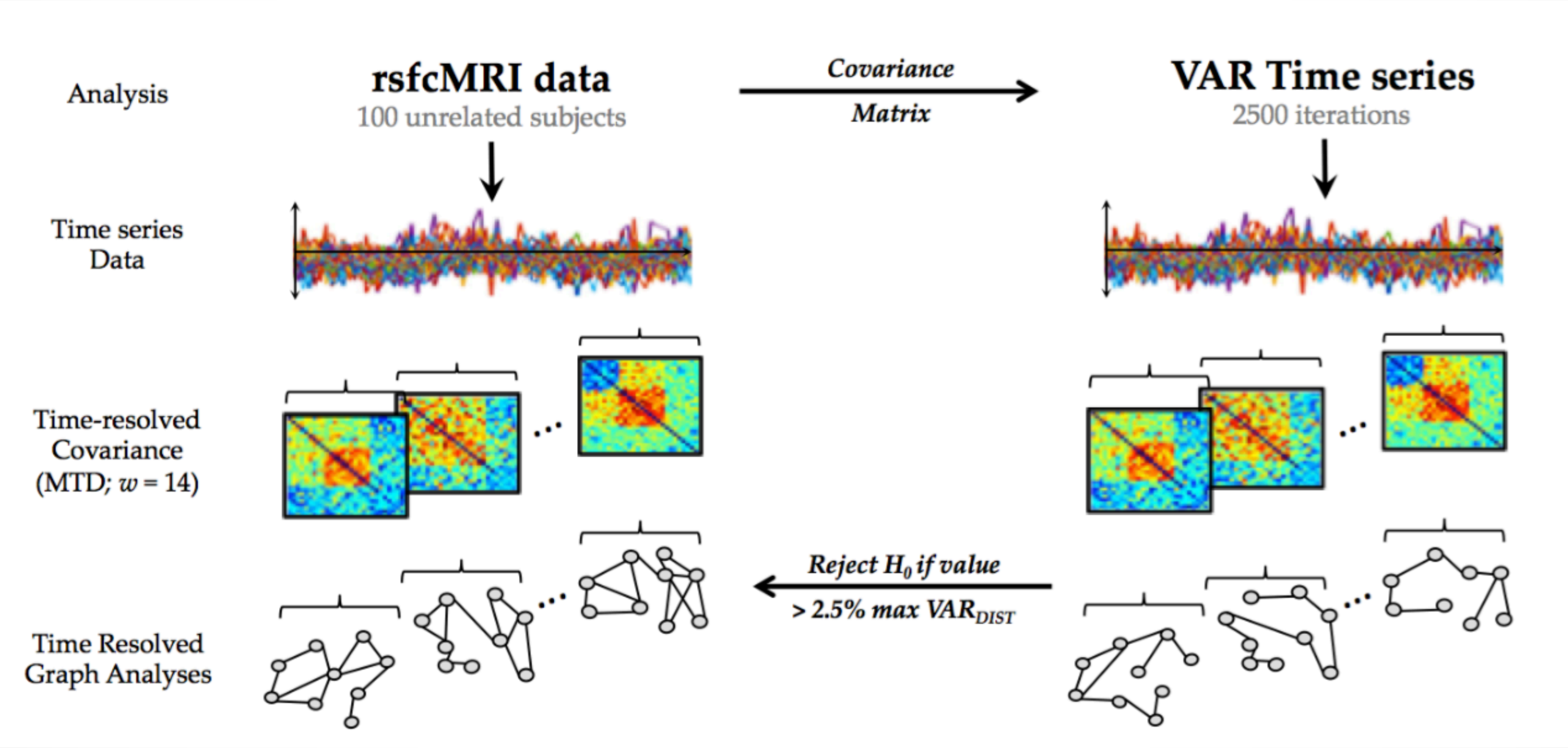
- **Non-parametric approach**: generate multiple synthetic time series that are matched to the time averaged connectivity e.g. from vector auto-regressive (VAR) model with matched static connectivity
- Compare statistics from stationary model with statistics from the presumed dynamic model using standard non-parametric one-sample test



Example from Zalesky et. al. (2014)



Example from Zalesky et. al. (2014)



Example from Shine et. al. (2016), Submitted

Conclusion

- Discussed parametric vs. nonparametric approaches for modeling temporal variation
  - Standard tradeoffs between parametric vs. non-parametric estimators
- Discussed model summary using clustering and cartographic profiling
  - also useful for parametric evolution models
- Discussed inference using parametric techniques (in a few cases) or non-parametric techniques

Tutorial References

- Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della Penna, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., et al. (2013). Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80, 360–378
- Calhoun, V. D., Miller, R., Pearlson, G., & Adalı, T. (2014). The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron, 84(2), 262-274

Software

- Discrete Hidden Markov Models: https://github.com/hmmlearn/hmmlearn
- MTD: https://github.com/macshine/coupling
- DCC (Lindquist): https://github.com/canlab/Lindquist_Dynamic_Correlation

Thank You!!!

Questions?

contact: sanmi@illinois.edu

References-I

- Calhoun, V. D., Miller, R., Pearlson, G., & Adalı, T. (2014). The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. Neuron, 84(2), 262-274.
- Ma, S., Calhoun, V. D., Phlypo, R., & Adalı, T. (2014). Dynamic changes of spatial functional network connectivity in healthy individuals and schizophrenia patients using independent vector analysis. Neuroimage, 90, 196-206.
- Rashid, B., Damaraju, E., Pearlson, G. D., & Calhoun, V. D. (2014). Dynamic connectivity states estimated from resting fMRI Identify differences among Schizophrenia, bipolar disorder, and healthy control subjects. Frontiers in human neuroscience, 8, 897.
- Lindquist, M. A., Xu, Y., Nebel, M. B., & Caffo, B. S. (2014). Evaluating dynamic bivariate correlations in resting-state fMRI: A comparison study and a new approach. Neuroimage, 101, 531-546.
- Nielsen, S. F. V., Madsen, K. H., Røge, R., Schmidt, M. N., & Mørup, M. (2015). Nonparametric modeling of dynamic functional connectivity in fmri data. In Proceedings of the 5th NIPS Workshop on Machine Learning and Interpretation in Neuroimaging (MLINI 2015).
- Engle, R. F., & Sheppard, K. (2001). Theoretical and empirical properties of dynamic conditional correlation multivariate GARCH (No. w8554). National Bureau of Economic Research.

References-II

- Shine, J. M., Koyejo, O., Bell, P. T., Gorgolewski, K. J., Gilat, M., & Poldrack, R. A. (2015). Estimation of dynamic functional connectivity using Multiplication of Temporal Derivatives. NeuroImage, 122, 399-407.
- Cribben, I., Haraldsdottir, R., Atlas, L. Y., Wager, T. D., & Lindquist, M. A. (2012). Dynamic connectivity regression: determining state-related changes in brain connectivity. Neuroimage, 61(4), 907-920.
- Hutchison, R. M., Womelsdorf, T., Allen, E. A., Bandettini, P. A., Calhoun, V. D., Corbetta, M., ... & Handwerker, D. A. (2013). Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage, 80, 360-378.
- Ryali, S., Supekar, K., Chen, T., Cai, W., Menon, V., (2015). A variational Bayes hidden Markov model for discovering dynamical functional brain networks. OHBM Poster & Talk
- Andersen, J. M., Koyejo, O., & Poldrack, R. A. (2016). Model-based dynamic resting state functional connectivity. Under preparation, OHBM 2016 poster
- Shine, J. M., Bell, P. T., Koyejo, O., Gorgolewski, K. J., Moodie, C. A., & Poldrack, R. A. (2015). Dynamic fluctuations in integration and segregation within the human functional connectome. arXiv preprint arXiv:1511.02976.

References-III

- Wang, J., & Kolar, M. (2014). Inference for Sparse Conditional Precision Matrices. arXiv preprint arXiv: 1412.7638.
- Lu, Junwei, Mladen Kolar, and Han Liu. "Post-regularization Inference for Dynamic Nonparanormal Graphical Models." arXiv preprint arXiv:1512.08298 (2015).
- Zalesky, A., Fornito, A., Cocchi, L., Gollo, L. L., & Breakspear, M. (2014). Time-resolved resting-state brain networks. Proceedings of the National Academy of Sciences, 111(28), 10341-10346.
- Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della Penna, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., et al. (2013). Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage 80, 360–378.