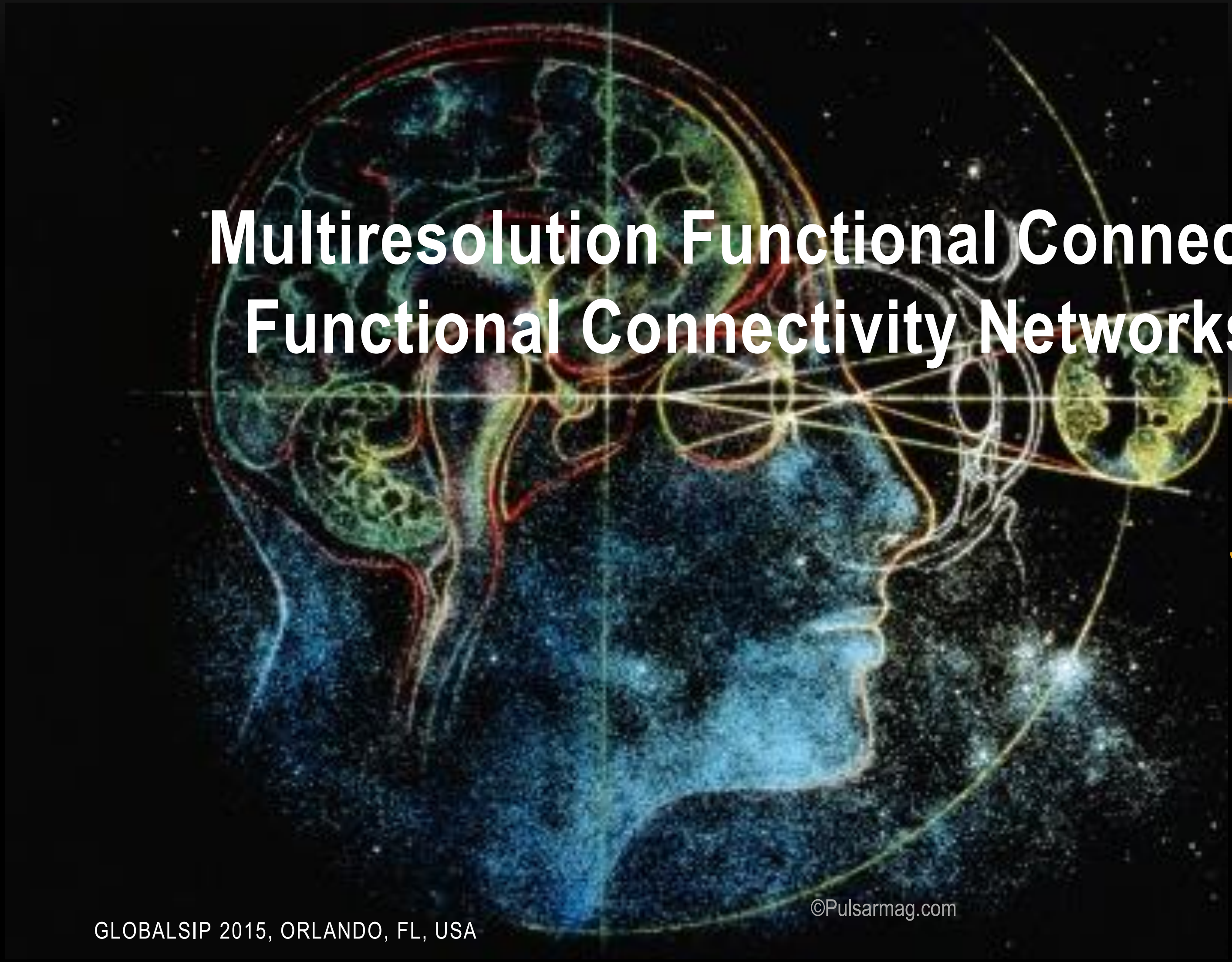

Multiresolution Functional Connectivity Analysis Refines Functional Connectivity Networks in Individual Brains

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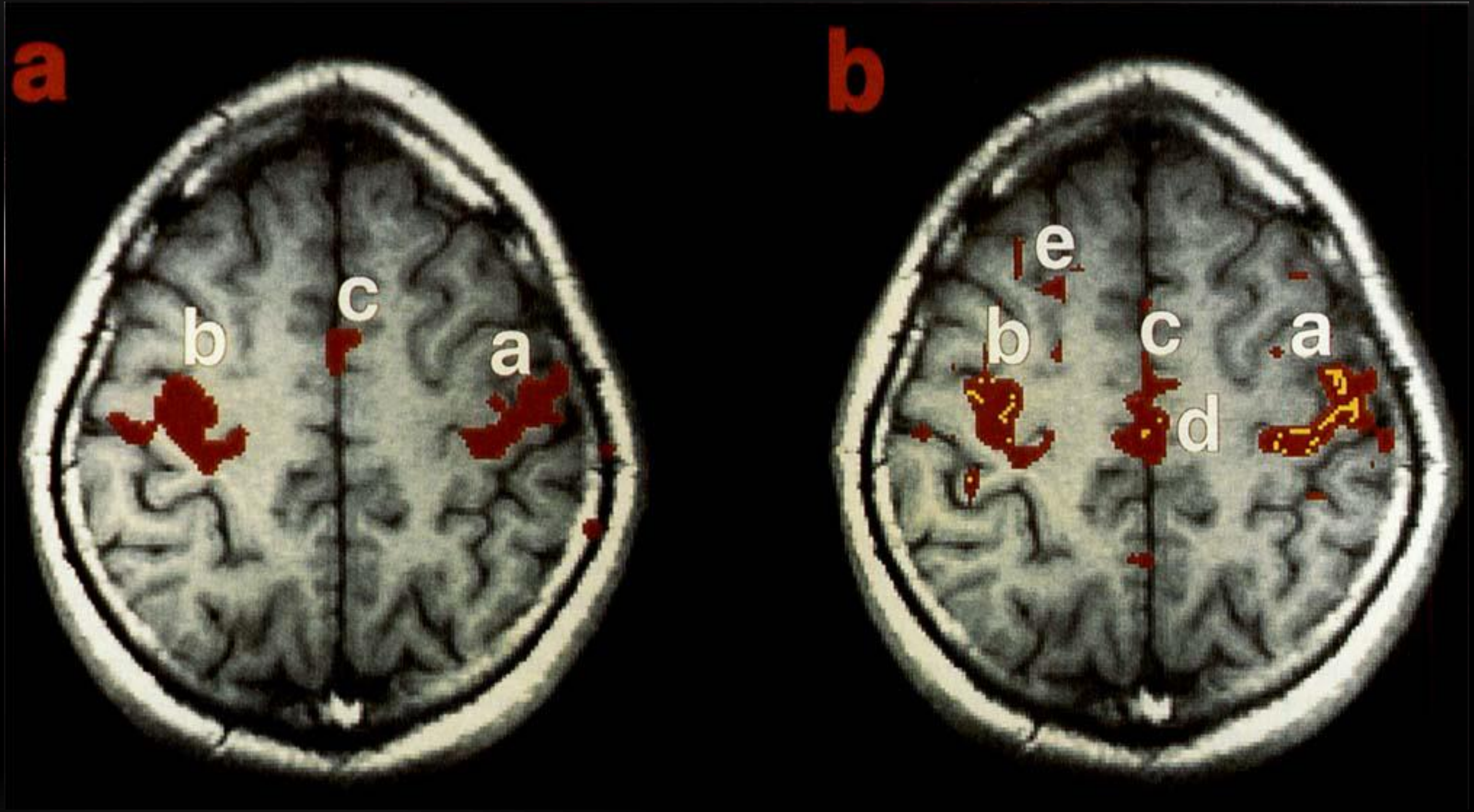
Outline

- Introduction
  - Functional connectivity functional magnetic resonance imaging (FC-fMRI)
  - Challenges and proposed solutions
- Initial Methods
  - Sub-band fractionation
  - Voxel clustering
- Initial Results
  - Our lab
  - Other labs
- Enhanced Methods
  - For network representation
  - For network aggregation
- Enhanced Results
- Conclusions

fc-fMRI

- Methodologically:
  - Infers relationships between regions during particular states.
  - Works with multiple datasets (EEG, LFP, fMRI, etc.)
  - And multiple algorithmic approaches (seed-based correlation to graph-theory)
- In application
  - Brain's intrinsic functional network architecture.
  - Changes associated with disease
  - Dynamic changes thru time

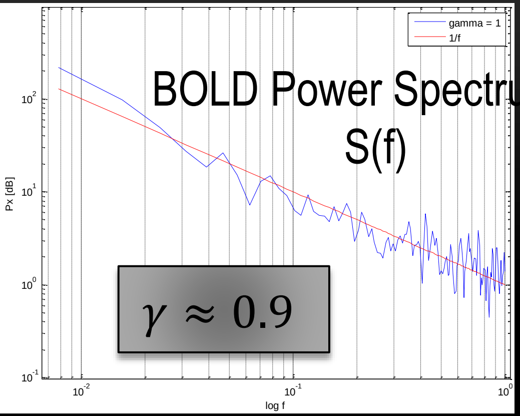


Biswal, B., et al. (1995). "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI." Magn Reson Med **34**(4): 537-541.

Challenges and Proposed Solutions

Challenges	Proposed solutions
Decouple overlapping BOLD signals	Signals should be transformed with a filter-bank: -wavelet packets
Depict network communications between both local and long range brain regions	Multi-spatial network analysis: -hierarchical clustering
Reduce manual work load interpreting multi-spatial and multi-spectral results	Features should be compared and aggregated into very similar feature sets: -wavelet entropy (signal level similarity) -mutual information (network level similarity)

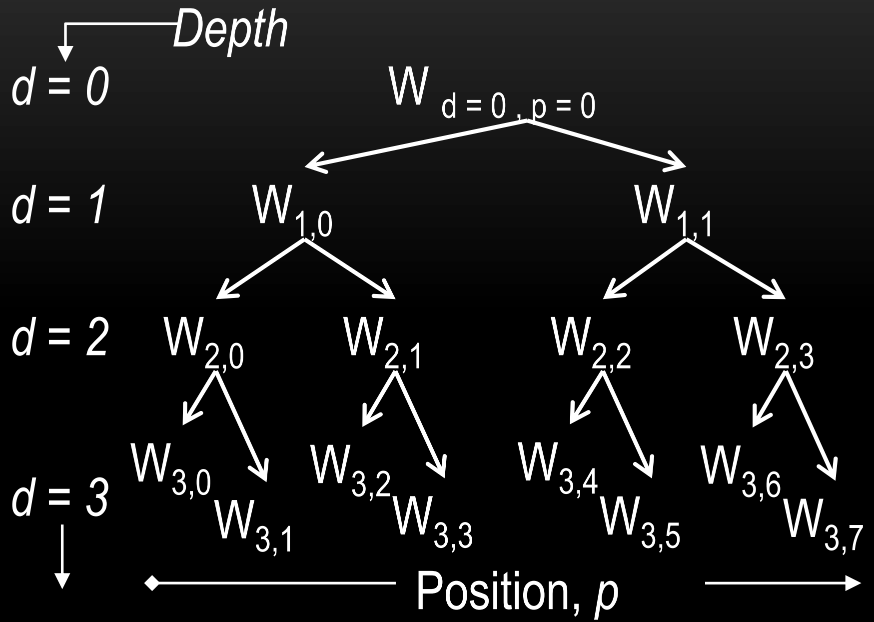
Signal Fractionation via the Wavelet Packet Transform

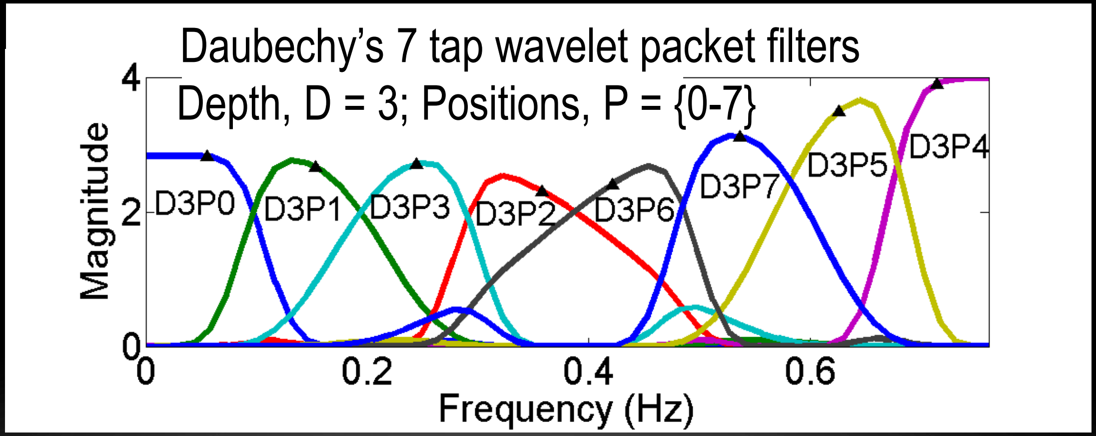


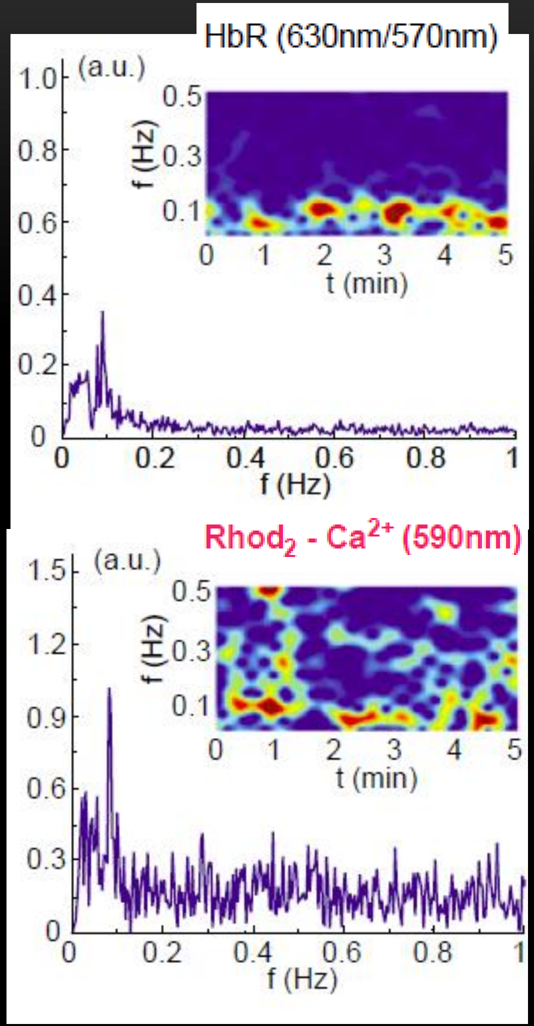
$$S(|f|) \approx \frac{1}{|f|^{\gamma}}$$

A. Medda, S. Keilholz. Wavelet Packet Based Clustering for the Study of Functional Connectivity in the Rat Brain. *Proceeding of the 46th Asilomar Conference on Signals, Systems, and Computers*; 2012 November 4, 2012; Pacific Grove, CA.

Wornell, G. W. (1993). "Wavelet-based representations for the 1/f family of fractal processes." Proceedings of the IEEE **81**(10): 1428-1450.

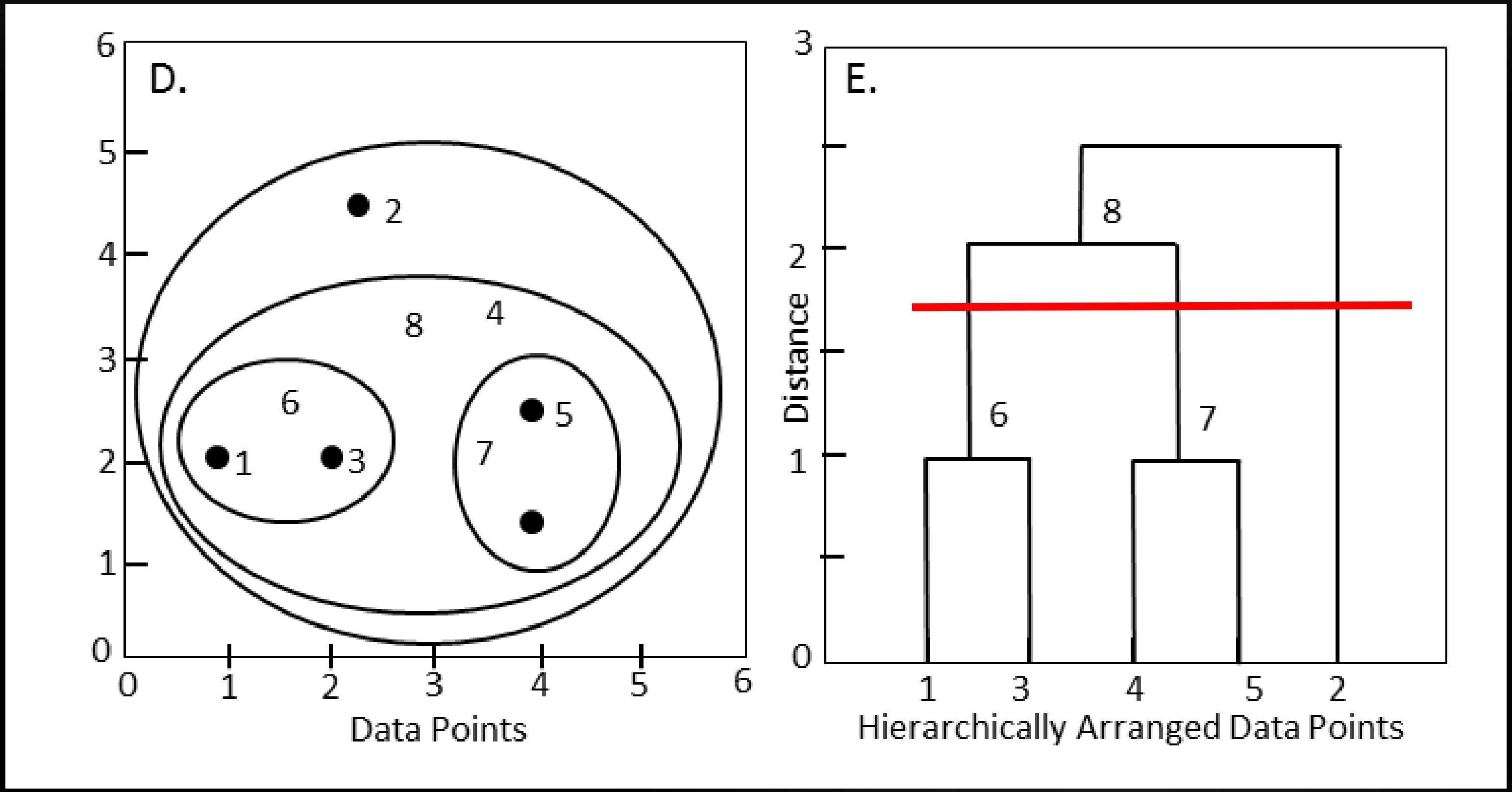






Du, C., et al. (2014). "Low-frequency calcium oscillations accompany deoxyhemoglobin oscillations in rat somatosensory cortex." Proc Natl Acad Sci U S A **111**(43): E4677-4686.

Hierarchical Clustering: A general utility for clustering information



- Distance Metric

$$S1(i,j) = \sqrt{\left(V_{i\neq j} - V_j\right)\left(V_{i\neq j} - V_j\right)^T},$$

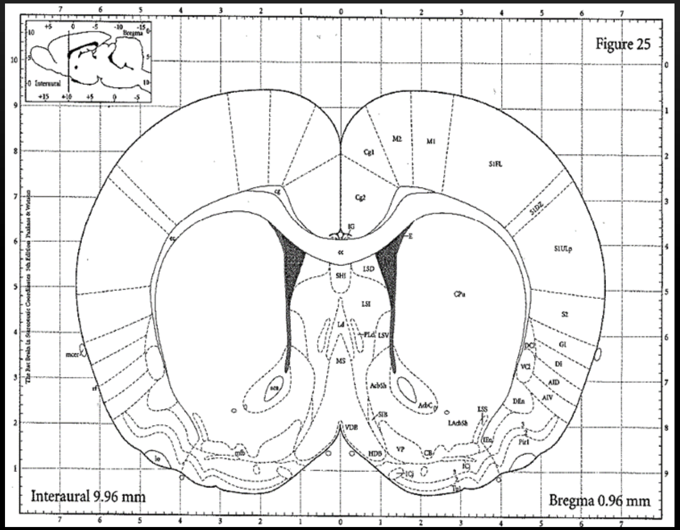
- Linkage Metric

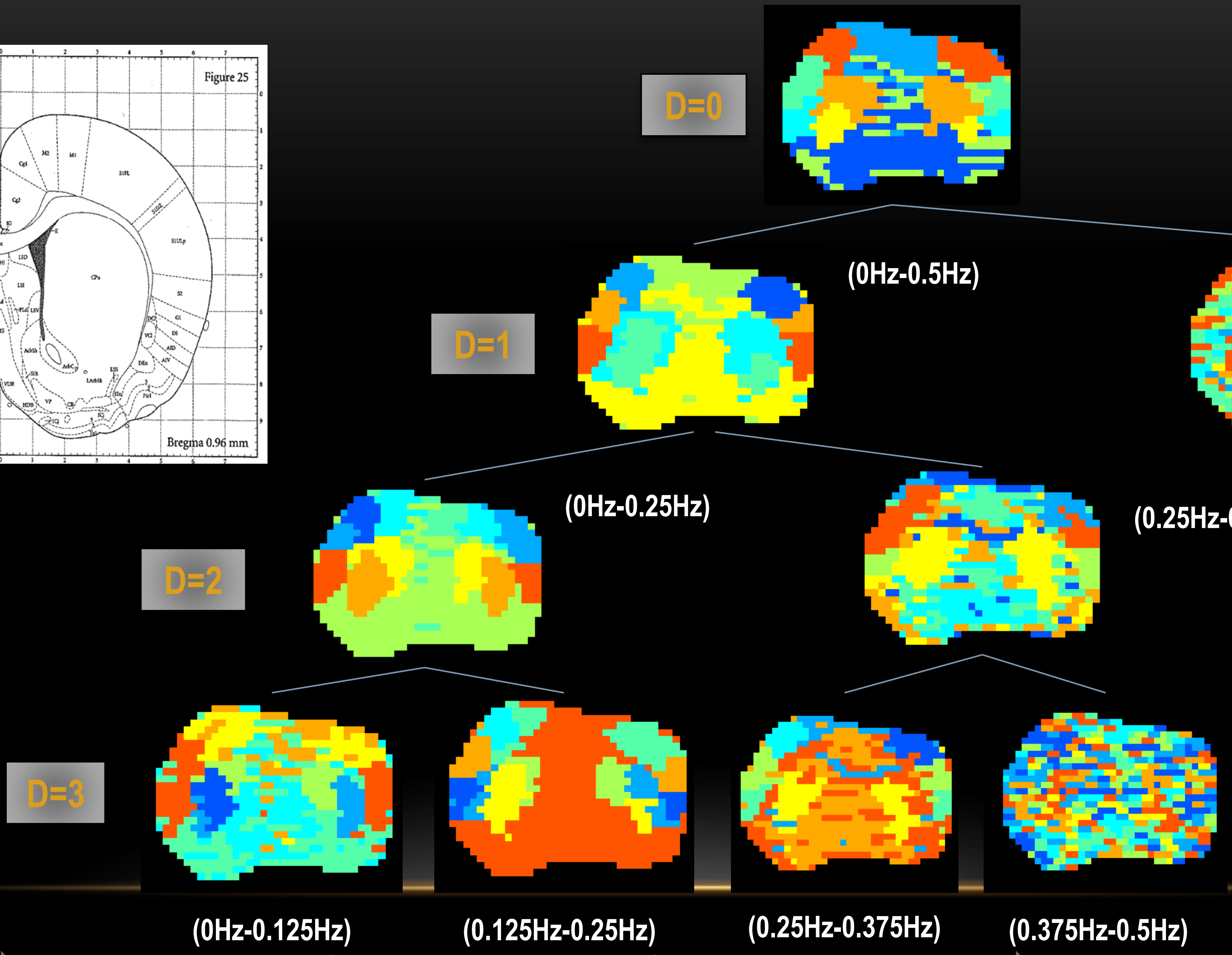
$$S2(a,b) = \frac{1}{(n_a n_b)} \sum_{i=1}^{n_a} \sum_{j=1}^{n_b} S1(i \in a, j \in b).$$

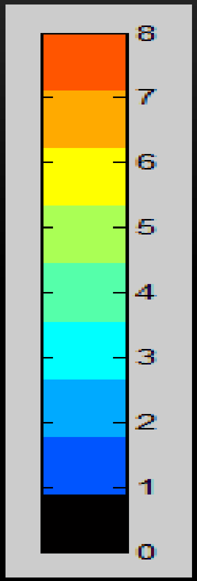
- Generation of the k[th] cluster

$$Y(k) = \min(S2_k)$$

Initial results on single slice of rat brain

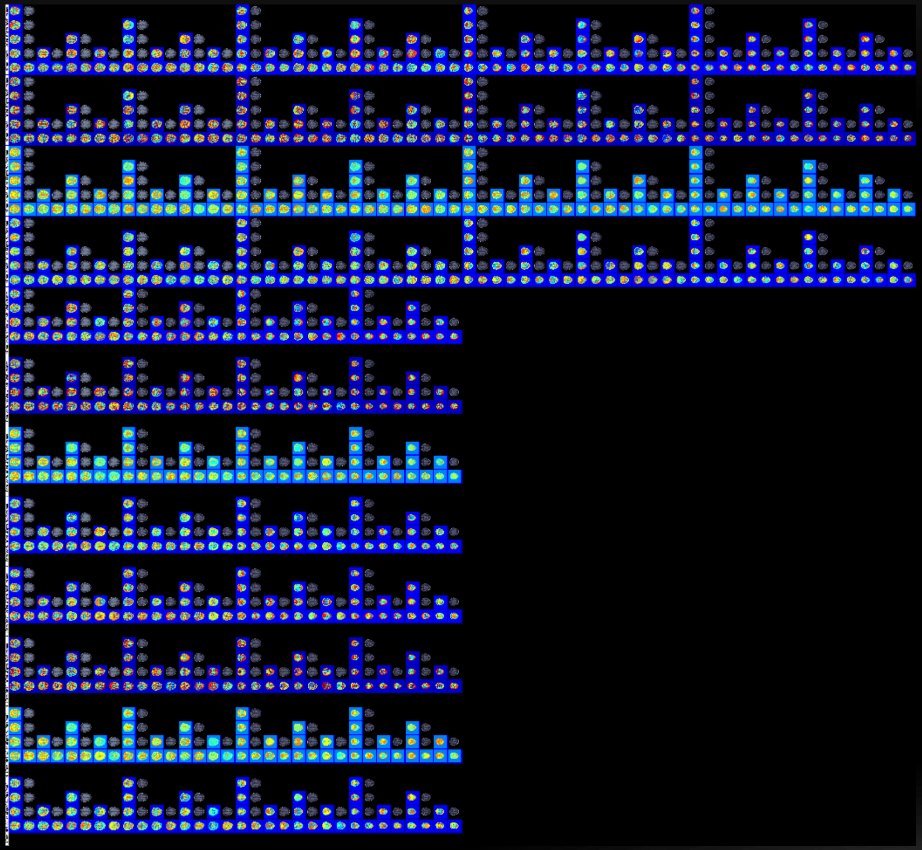


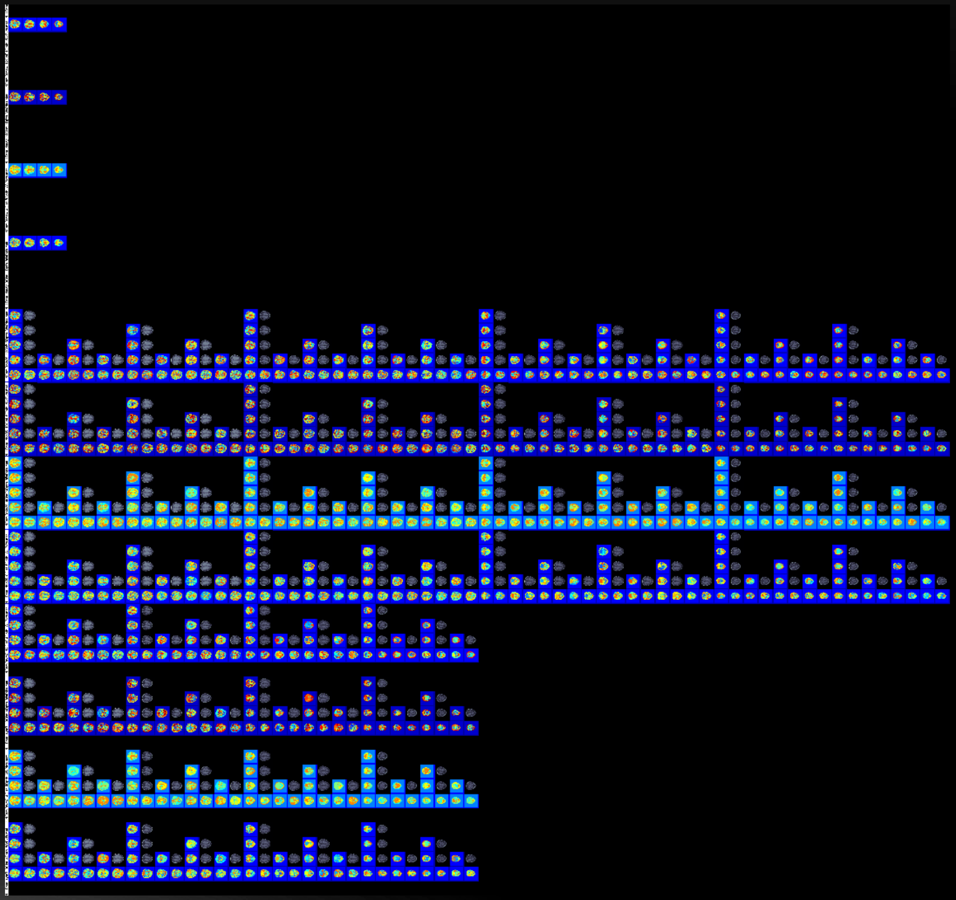




A. Medda, S. D. K. (2012). Wavelet Packet Based Clustering for the Study of Functional Connectivity in the Rat Brain. Proceeding of the 46th Asilomar Conference on Signals, Systems, and Computers, Pacific Grove, CA.

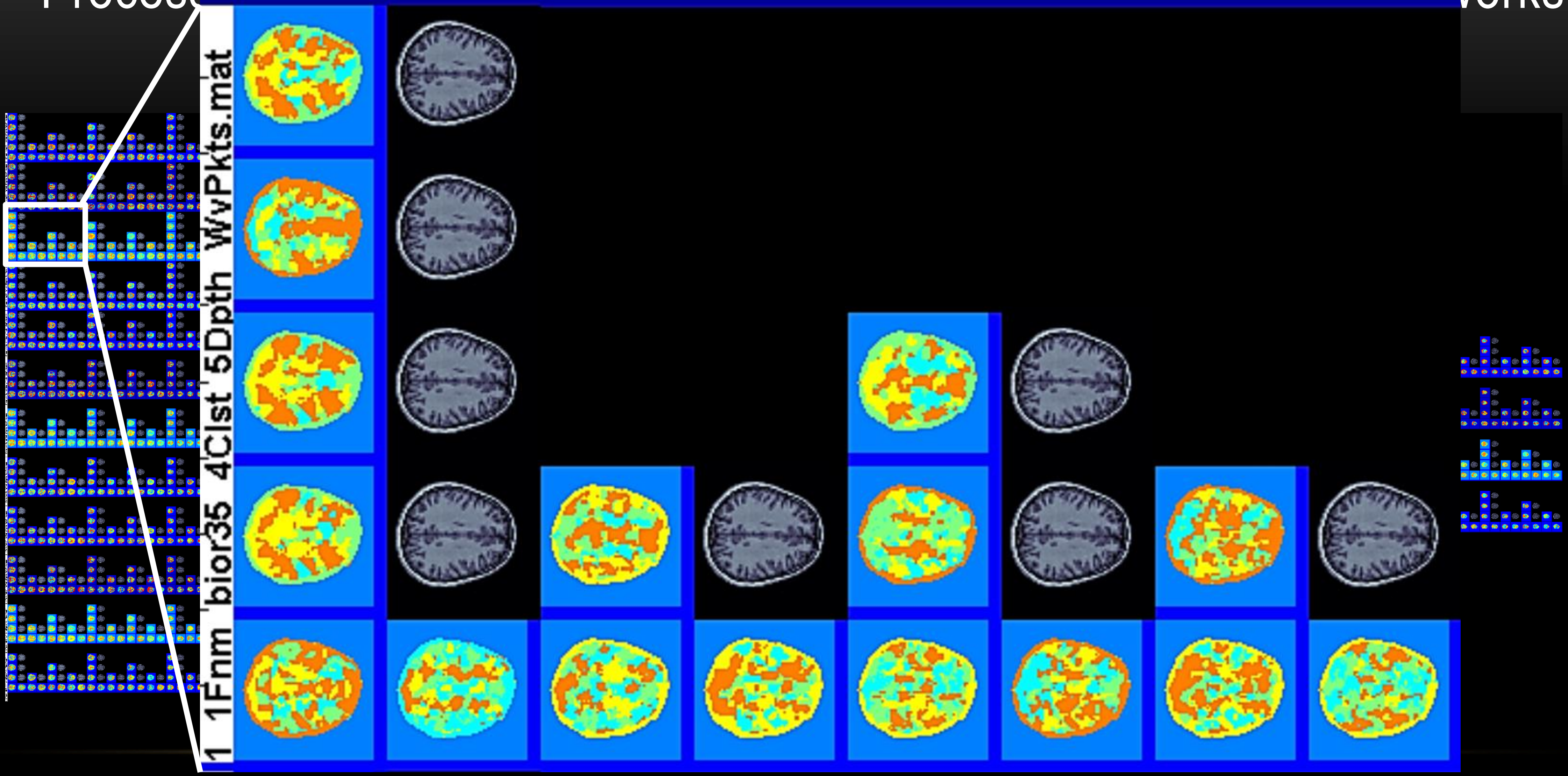
Process Explodes the Search Space for Functionally Relevant Networks



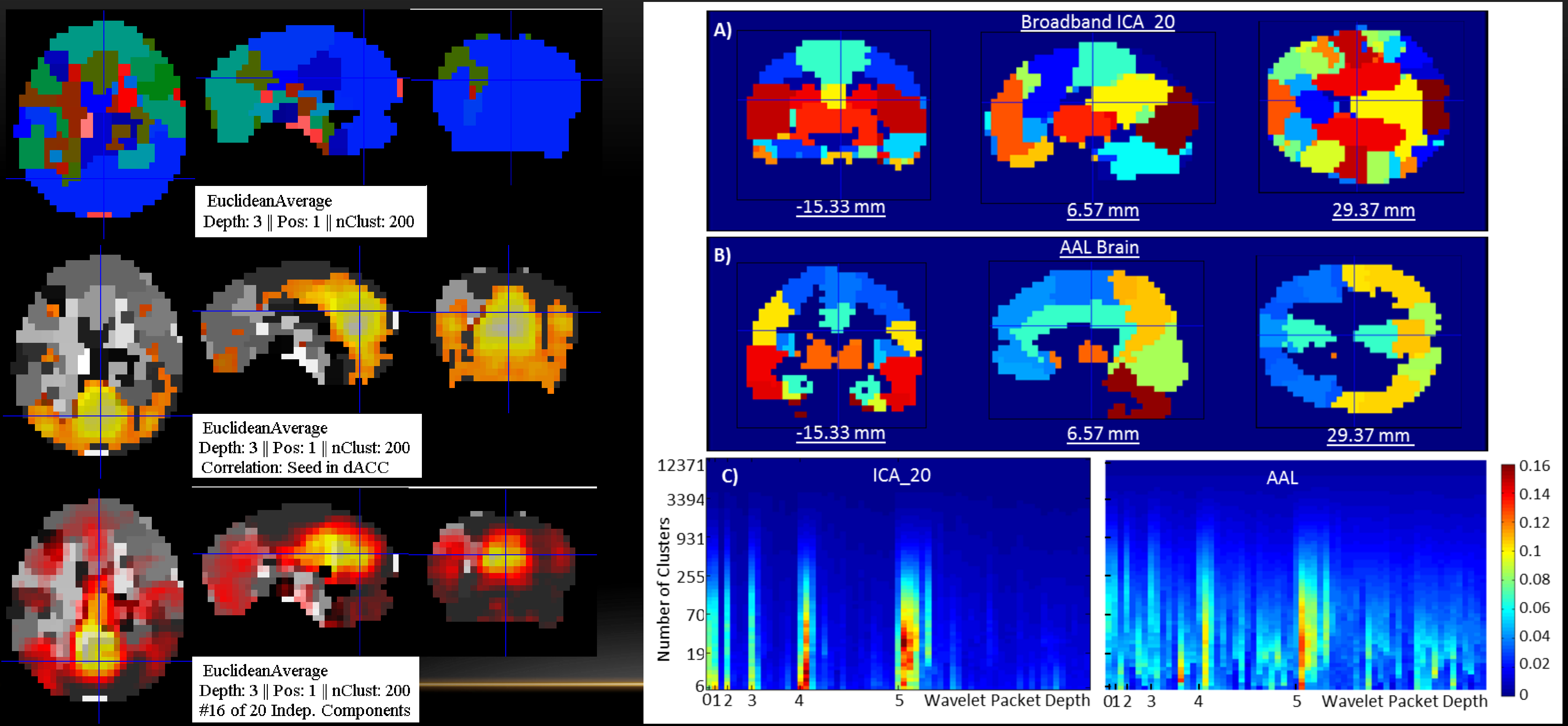


Introduction | Initial Methods | Initial Results | Enhanced Methods | Enhanced Results | Conclusions

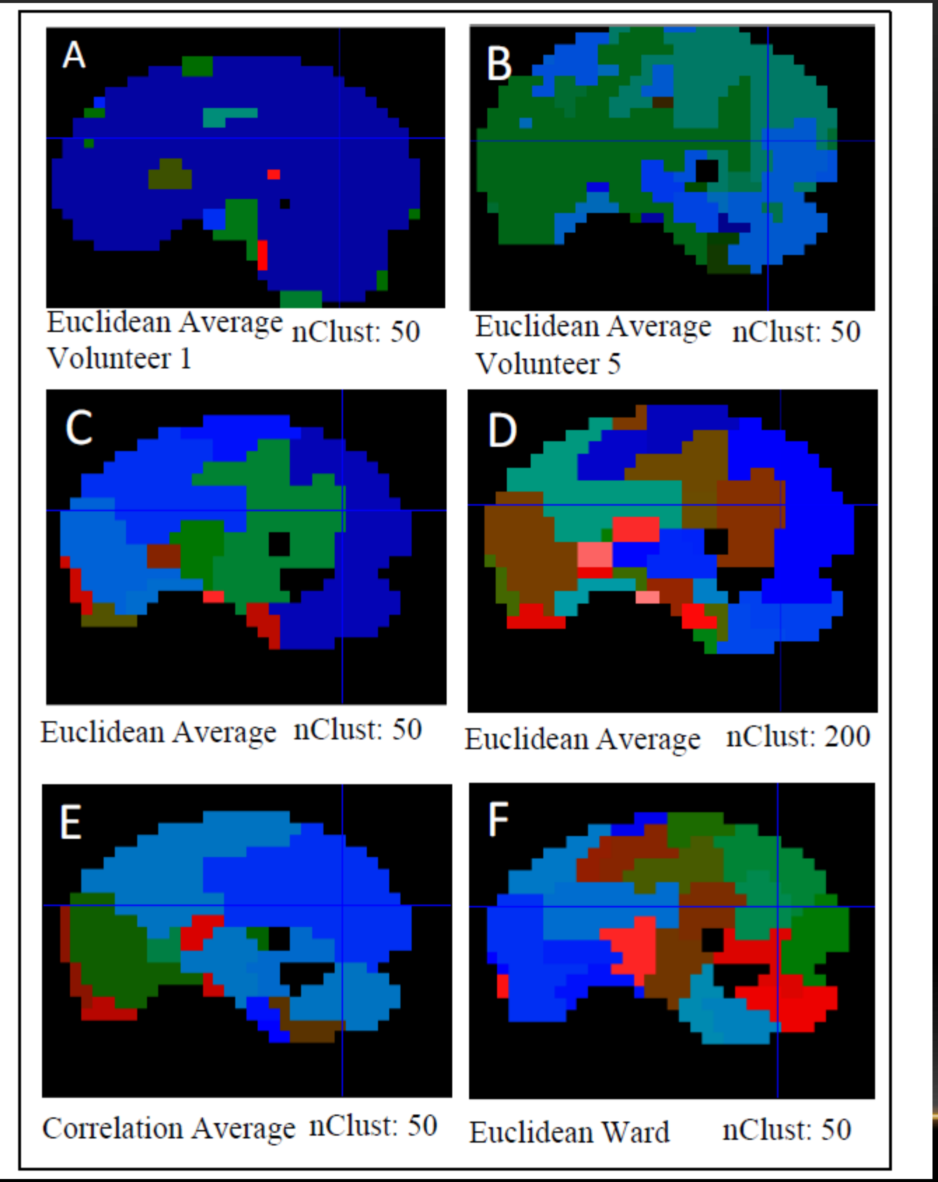
Process Explodes the Search Space for Functionally Relevant Networks



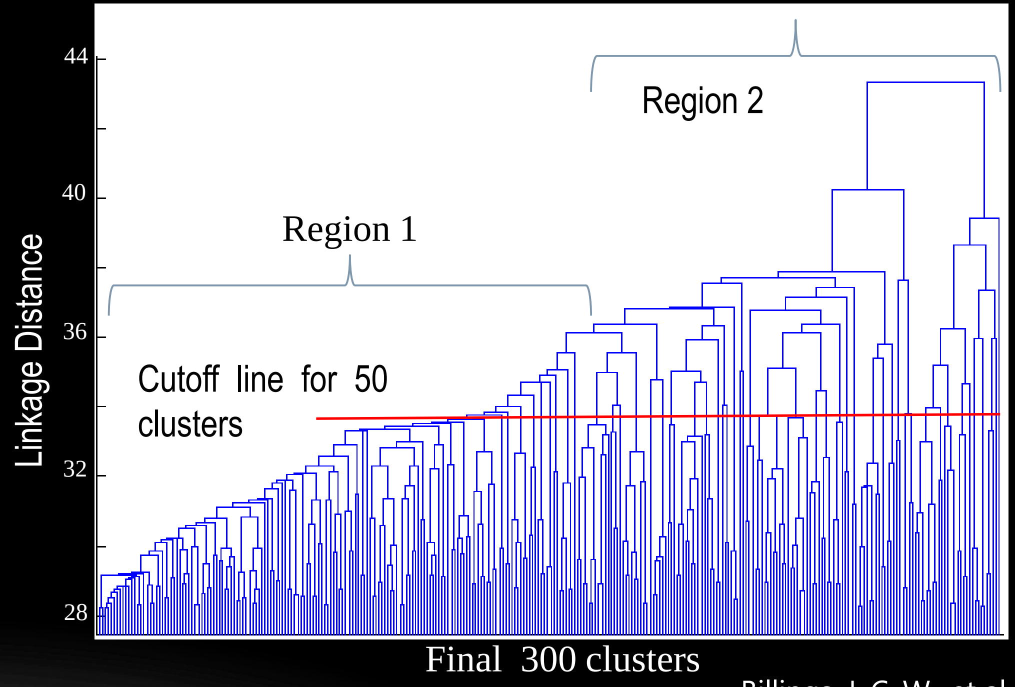
Wavelet Clustering fc-fMRI Compares Well with Alternative Techniques



Initial results in multi-slice human data

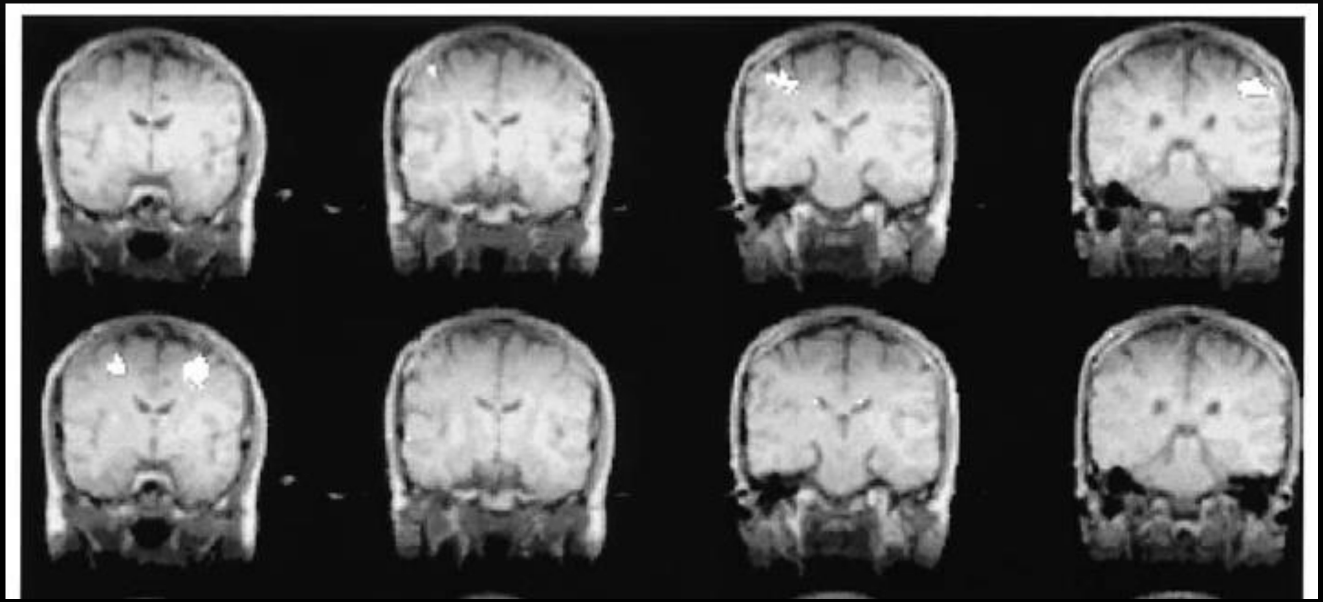


- Public resting-state BOLD dataset: NKI Enhanced Rockland Sample
- Hundreds of volunteers evenly sampled across demographic
- TR = 0.645 s, 3 mm isotropic, 10 minutes
- Standard preprocessing (SPM 8)

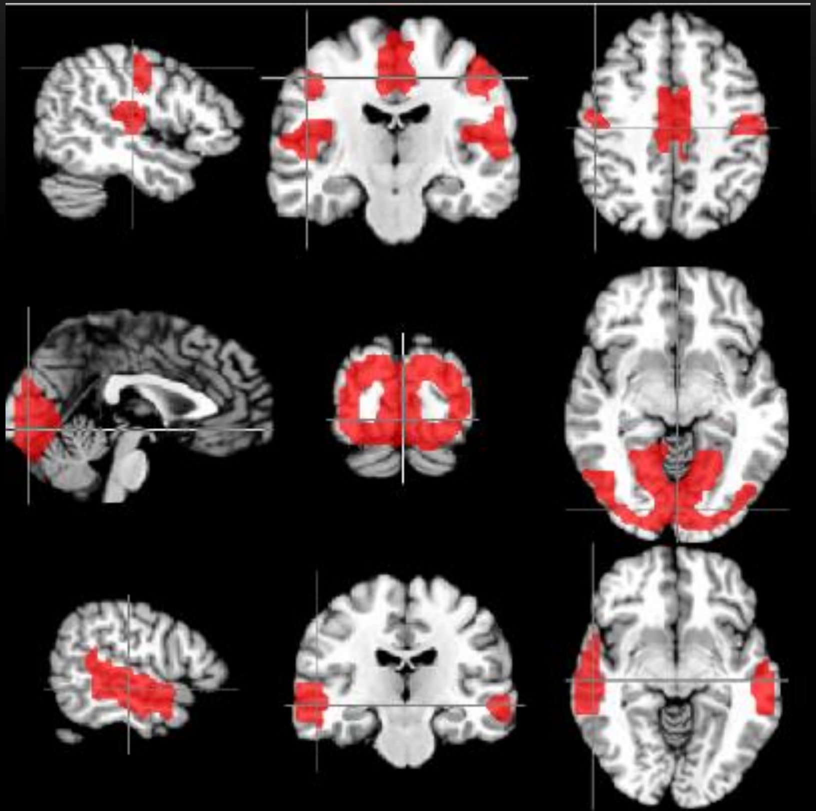


Billings, J. C. W., et al. (2013). Agglomerative clustering for resting state MRI. Neural Engineering (NER), 2013 6th International IEEE/EMBS Conference on.

Agglomerative clustering for whole-brain networks?

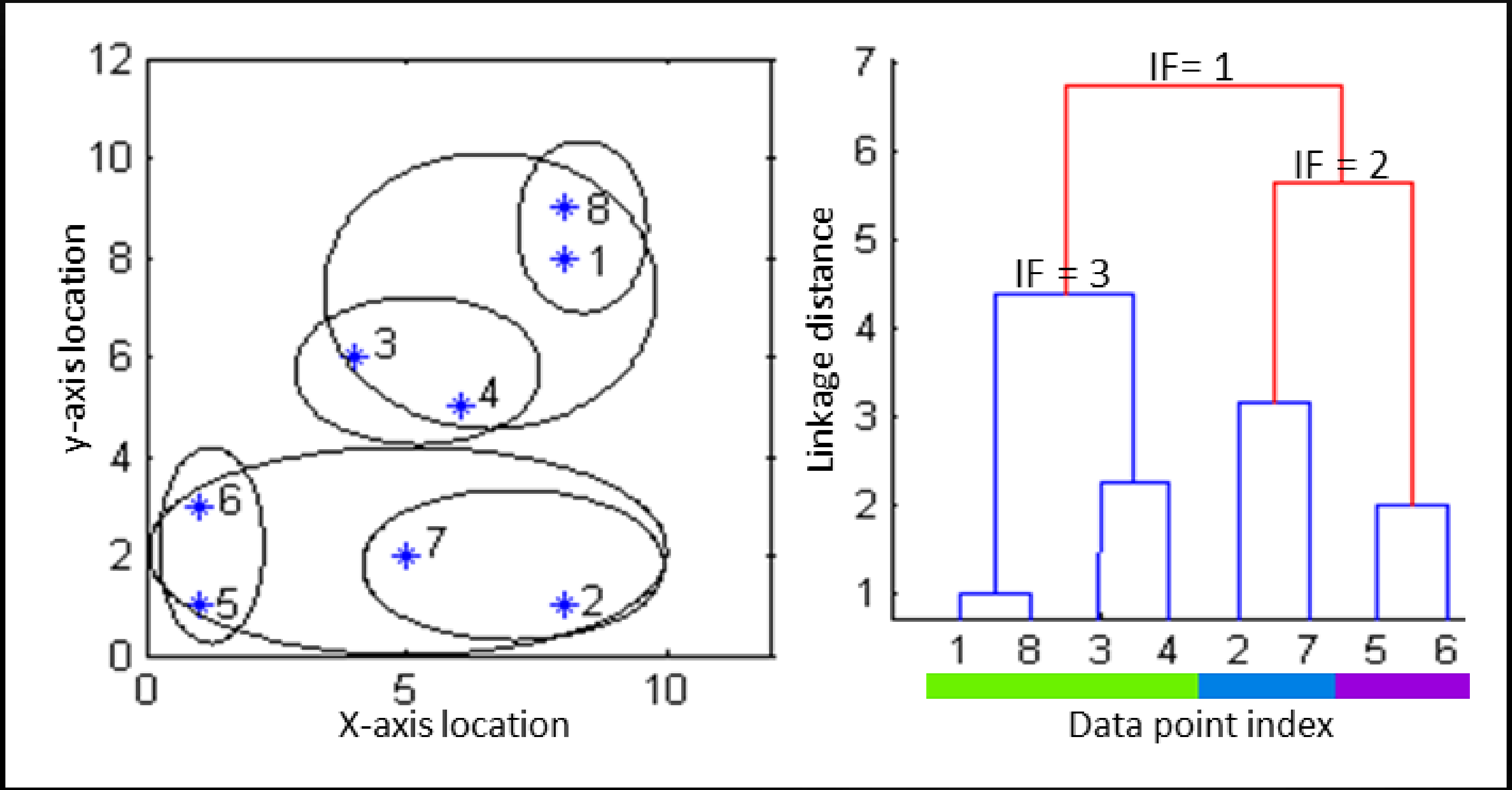


Cordes, D., et al. (2002). "Hierarchical clustering to measure connectivity in fMRI resting-state data." Magnetic resonance imaging **20**(4): 305-317.



Wang, Y. and T.-Q. Li (2013). "Analysis of Whole-Brain Resting-State fMRI Data Using Hierarchical Clustering Approach." PLoS ONE **8**(10): e76315.

An Improved Method for Cutting a Hierarchical Clustering Tree

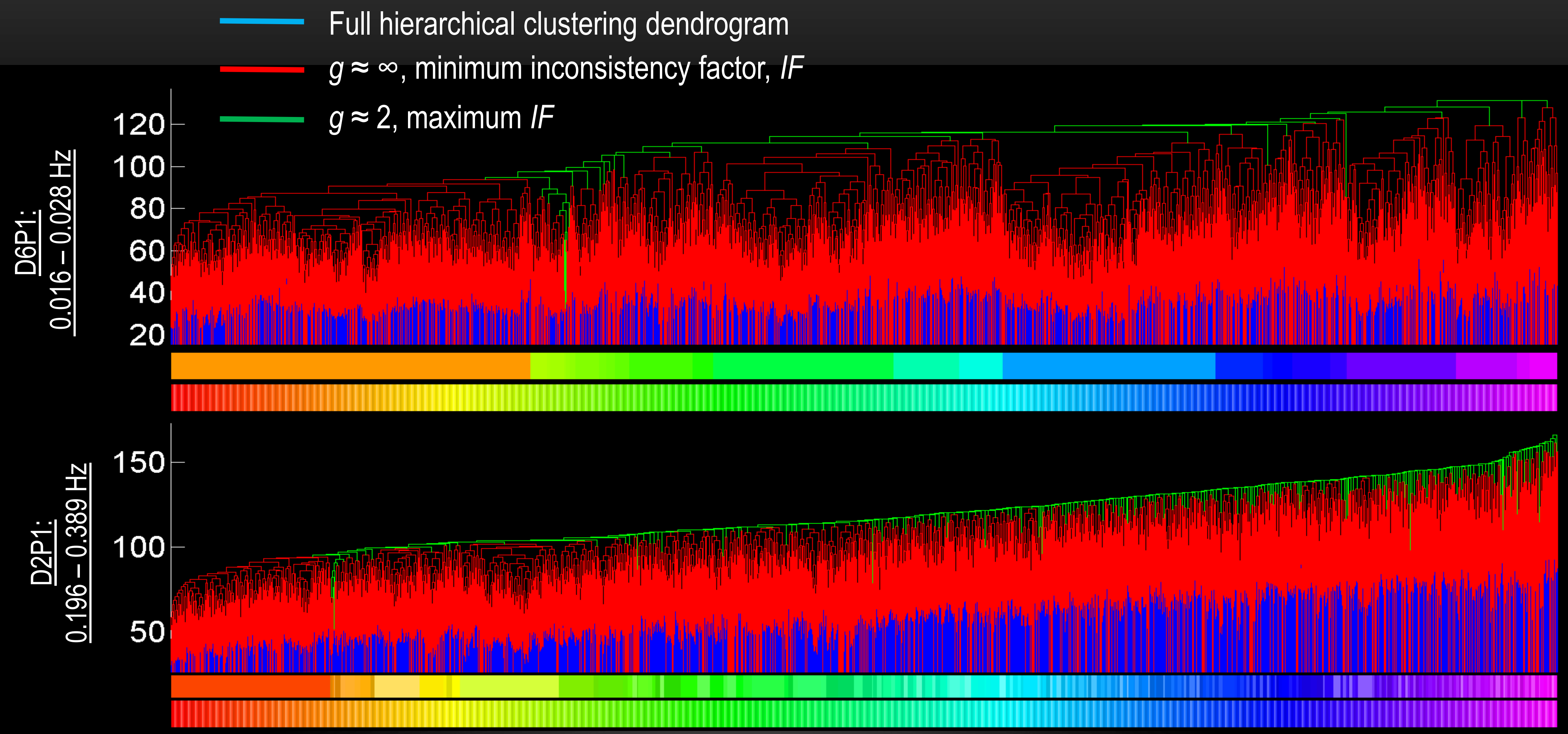


- The inconsistency factor cuts the hierarchy

$$IF(Y_k) = \left(Y_k - \bar{Y}_g\right)/std(Y_g)$$

Subscript *g* is the number of links for which an average and standard deviation are calculated.

The Hierarchical Clustering Dendrogram is a Natural Space for Conveying Network Multi-Scalability, n = 112



Feature comparison and aggregation

Signal comparisons

- *Non-normalized Shannon Entropy*

$$E(s) = -\sum_i s_i^2 \log\left(s_i^2\right)$$

With s_i being a voxel's wavelet coefficients

Network comparisons

- *Cluster Entropy:*

$H(C) = -\sum_{i=1}^{k} P(i) \log_2 P(i)$,
with $P(i) = \frac{|C_i|}{n}$,
C_i is a cluster of n parts.

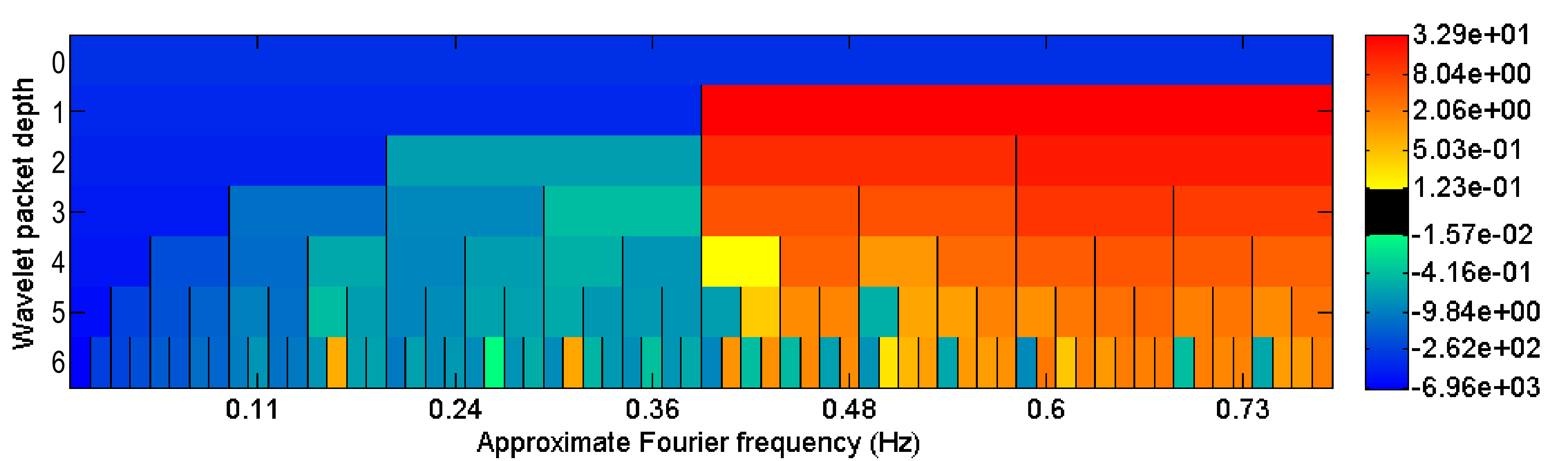
- *Mutual information:*

$I(C', C'') = \sum_{i=1}^{k} \sum_{j=1}^{l} P(i,j) \log_2 \frac{P(i,j)}{P(i)P(j)}$,
where $P(i,j) = \frac{|C_i \cap C_j|}{n}$.

- Variation in information:

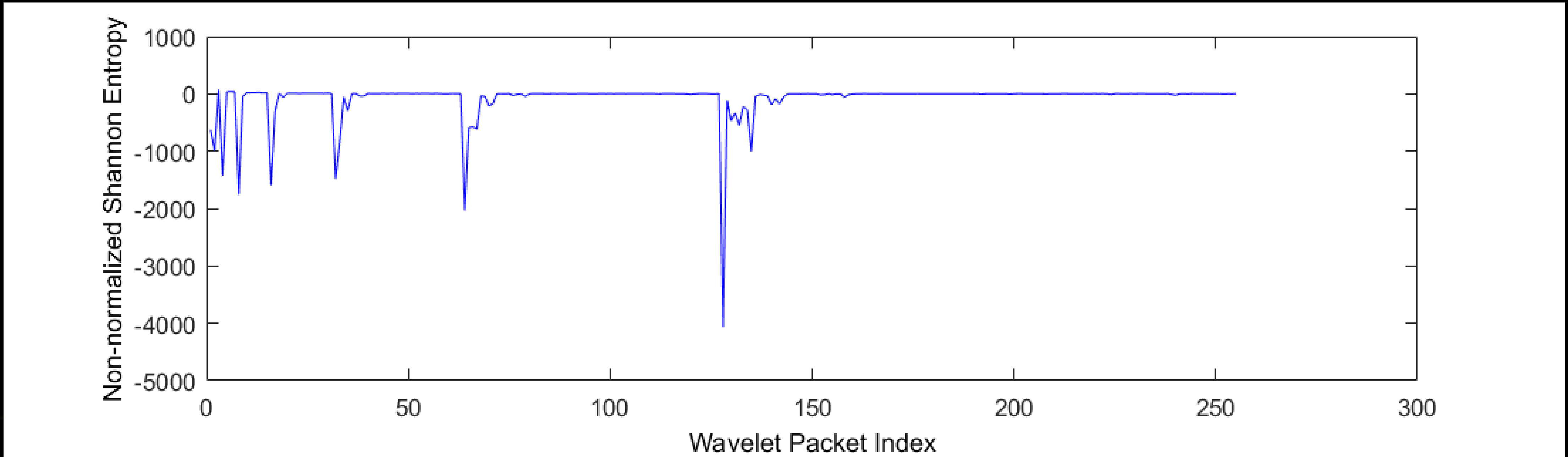
$\mathrm{VI}(C', C'') = \left[H(C') - I\left(C', C'\right)\right] + \left[H(C'') - I(C', C'')\right]$

Entropy values across spectra, N = 112

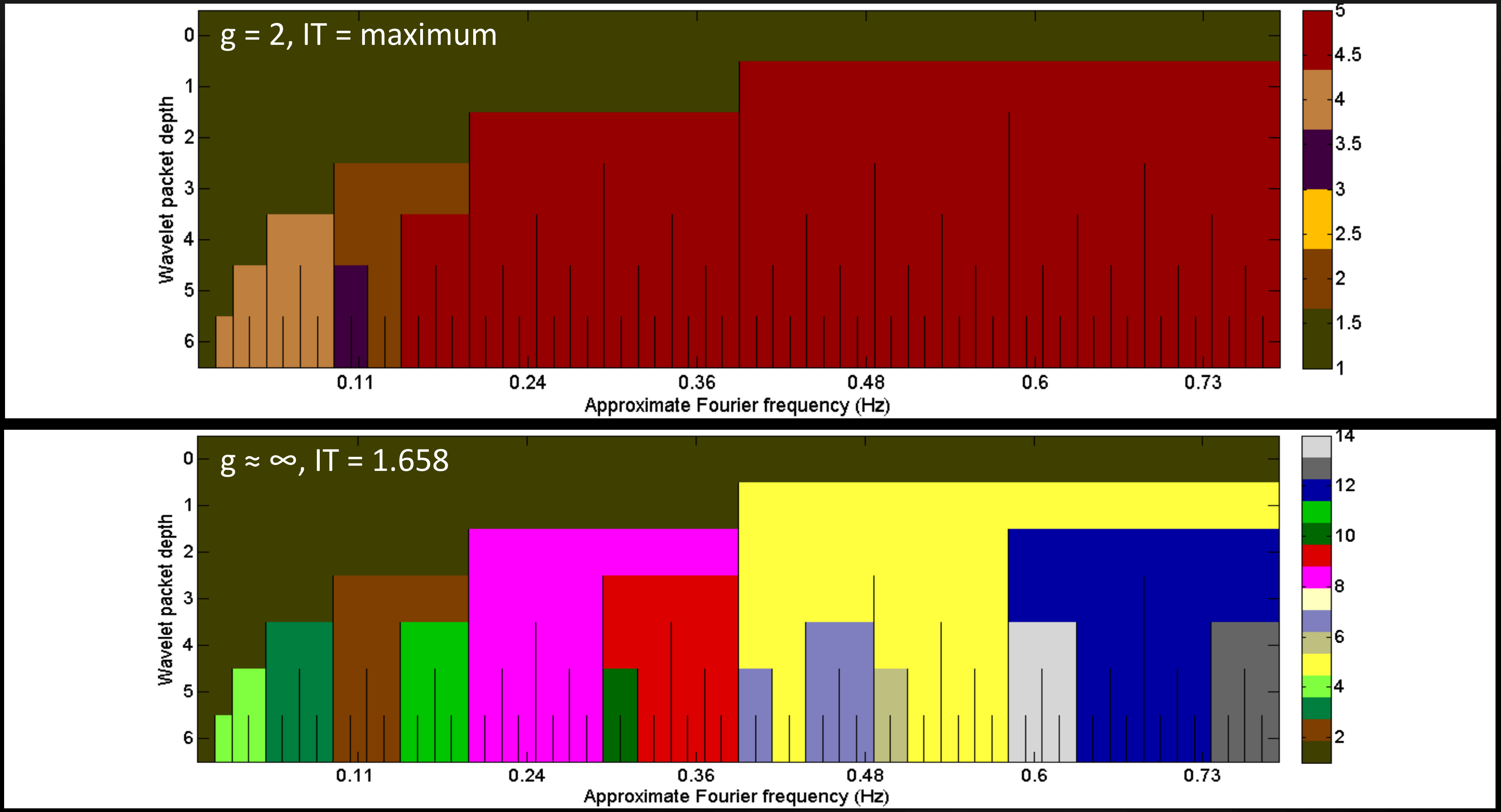


Non-normalized Shannon Entropy

$$E(s) = -\sum_i s_i^2 \log(s_i^2)$$



Network Spectral Similarity as Identified Through Mutual Information

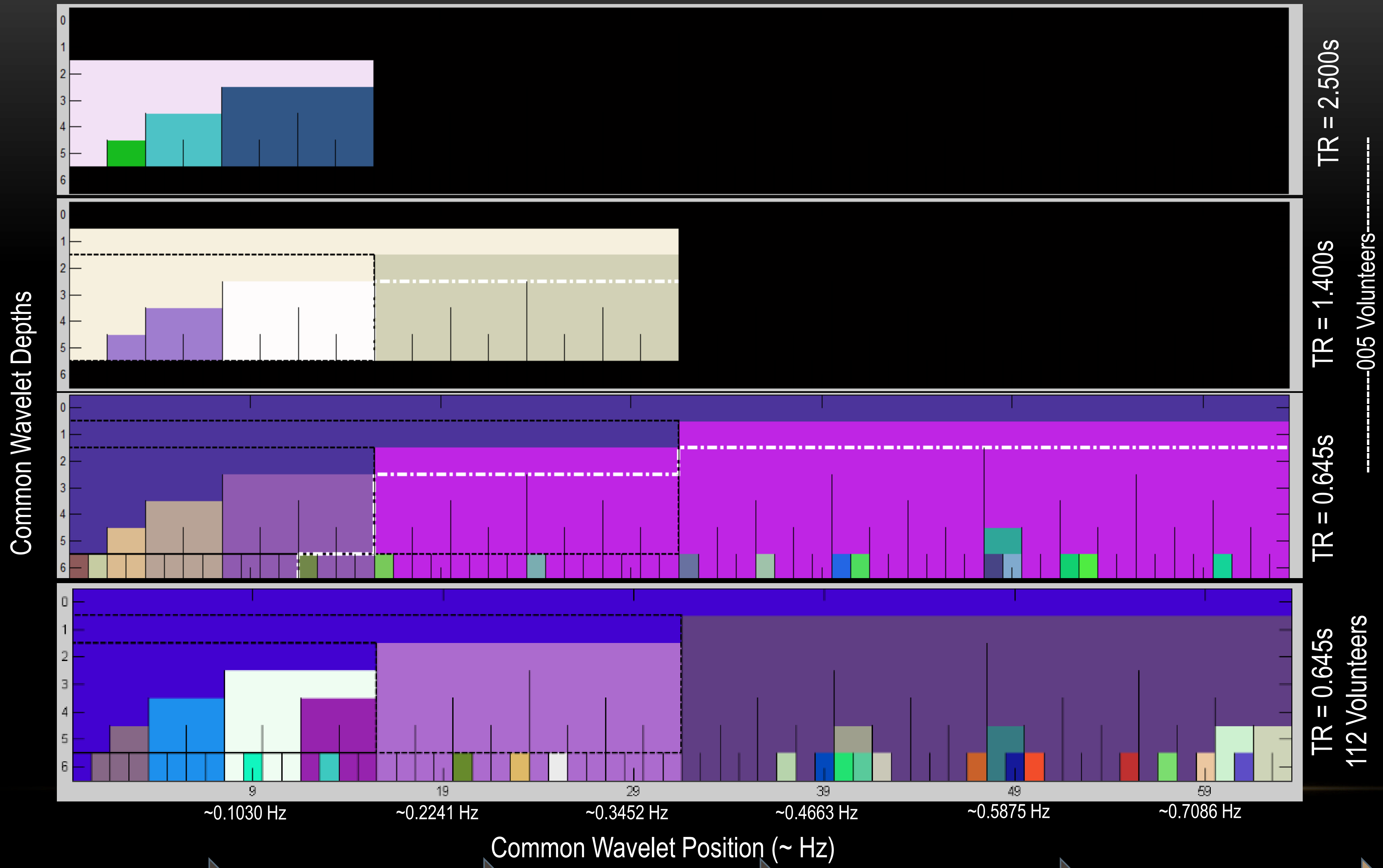


Entropy:
$H(C) = -\sum_{i=1}^{k} P(i)\log_2 P(i)$,
with $P(i) = \frac{|C_i|}{n}$,
C_i is a cluster of n parts.

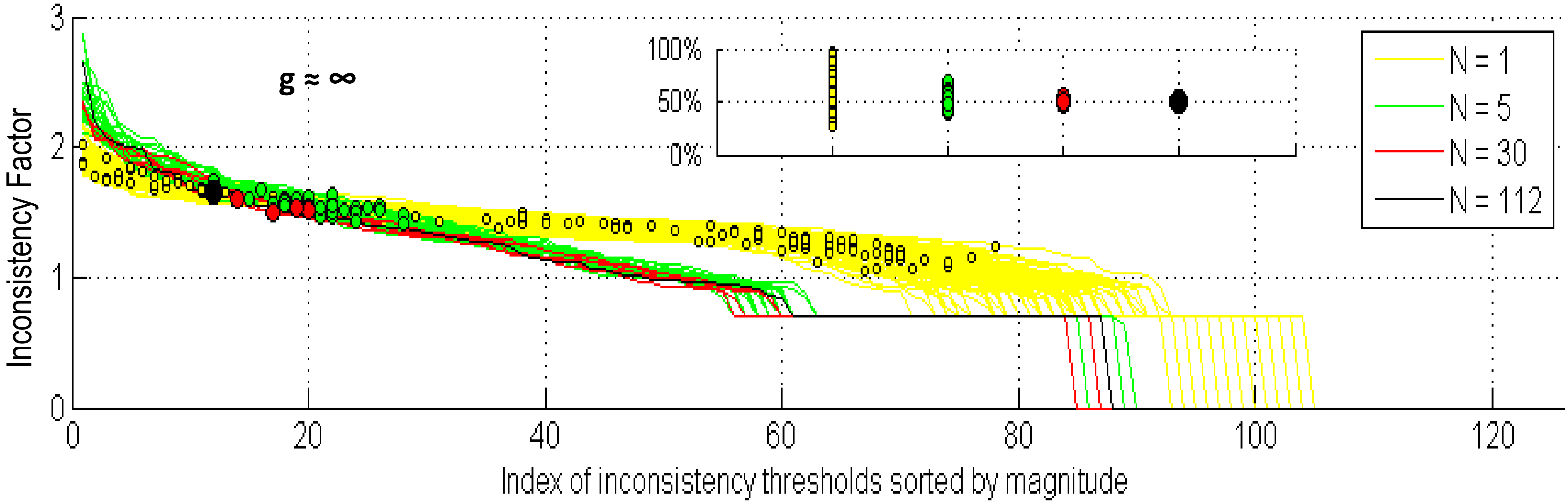
Mutual information:
$I(C', C'') =$
$\sum_{i=1}^{k}\sum_{j=1}^{l} P(i,j)\log_2 \frac{P(i,j)}{P(i)P(j)}$,
where $P(i,j) = \frac{|C_i \cap C_j|}{n}$.

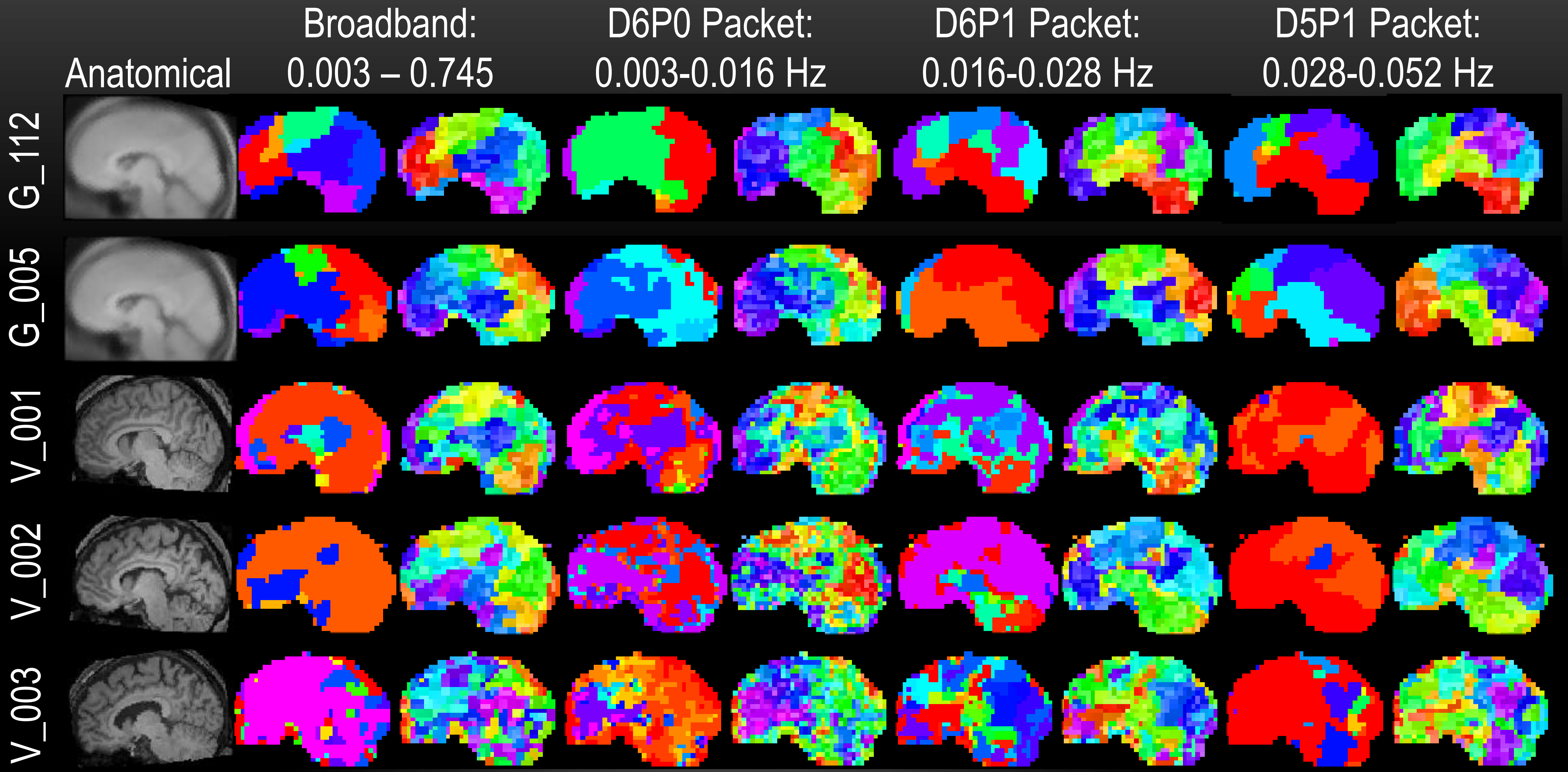
Variation in information:
$\mathrm{VI}(C', C'') =$
$[H(C') - I(C', C')] +$
$[H(C'') - I(C', C'')]$.

Network Spectral Similarity as Identified Through Mutual Information



The Low-frequency Fluctuation Domain Separates into Distinct Networks at the 50% Point of All Inconsistency Factors





G_###: Group dataset with ### volunteers
V_###: Volunteer ###

g = 2 max *IF*

g ≈ ∞ min *IF*

Conclusion

- BOLD signal <0.1 Hz has a high probability of containing a large amount of noise
- Best BOLD networks in the low-frequency fluctuation range between 0.01 and 0.1 Hz
- Frequency range may be subdivided into to build quantitatively distinct networks
- Functional connectivity networks exist at several spatial scales who complimentarily address whole brain connectivity
- Network connectivity in groups produce well known functional architecture
- Individual networks demonstrate a mixture of highly variant architectures in addition to well known network features
- Equivalent findings observed independent of acquisition parameters

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