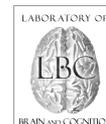


# Dynamic Resting State fMRI Assessment

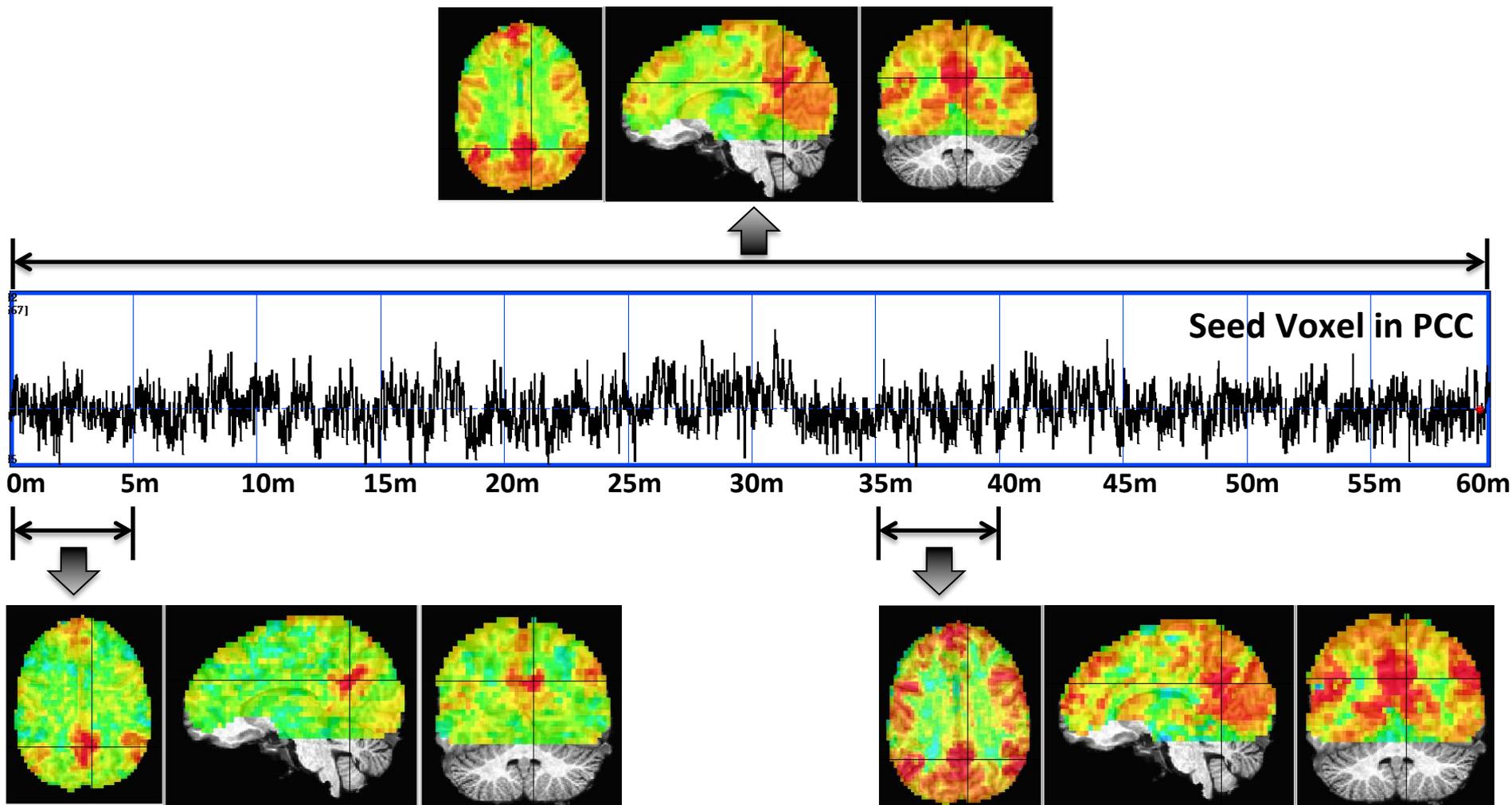
Javier González-Castillo

Section on Functional Imaging Methods, NIMH, NIH

August 2015, National Institutes of Health, Bethesda, MD

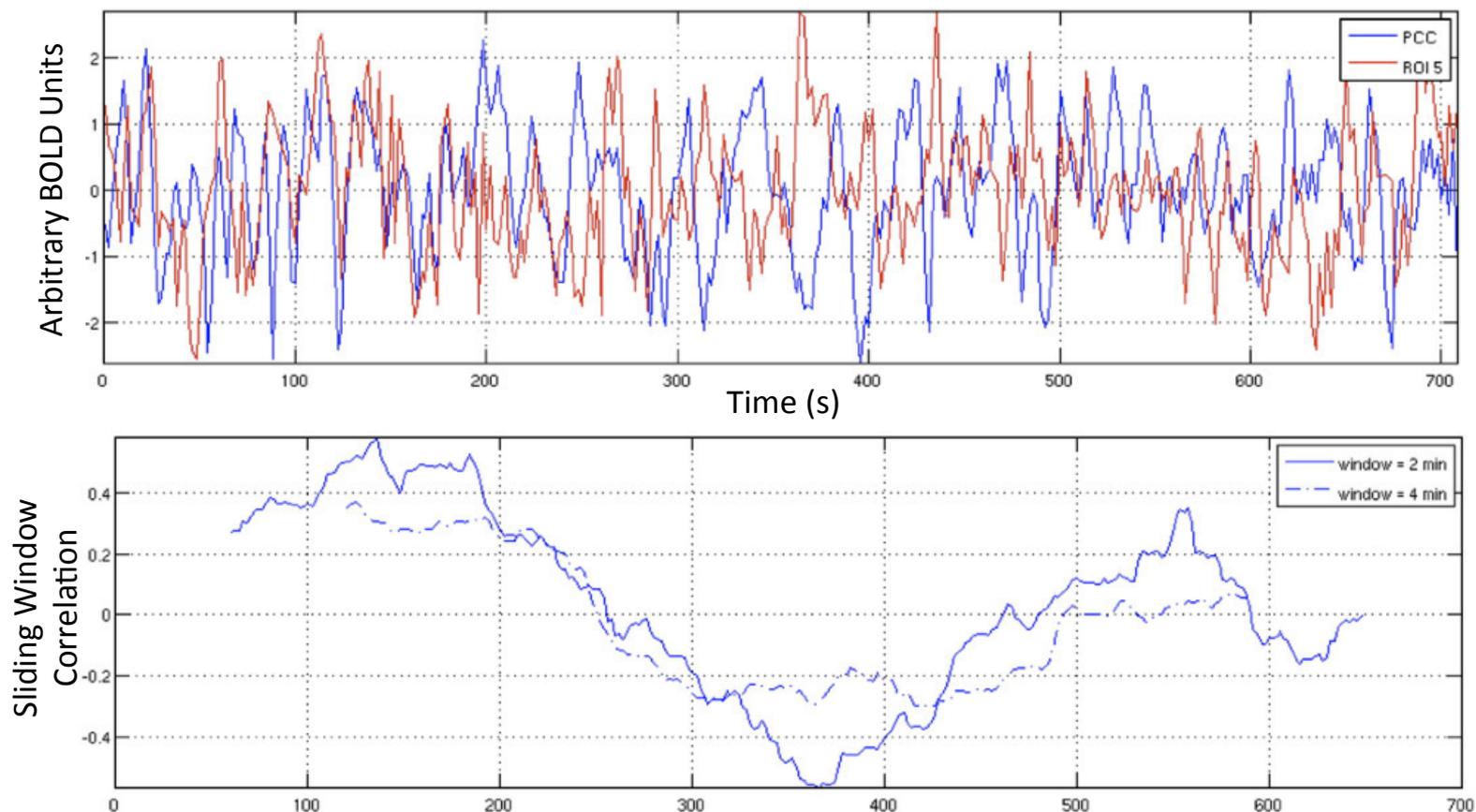


- **WHAT IS BOLD FUNCTIONAL CONNECTIVITY DYNAMICS?**
  - Original observations
  - Spatial Distribution
  - Relationship to Structural Connectivity
- **RELATIONSHIP TO COGNITION / DISEASE**
  - Sleep Staging based on Dynamic FC Changes.
  - Cognitive State Detection based on Dynamic FC Changes.
  - Disruption of Dynamic FC Patterns in patient populations.
- **SOME COMMENTS ON METHODOLOGY**
  - Interpretational Issues with Sliding Window Correlation
  - Dynamic Conditional Correlation (DCC)
  - Single-volume Co-Activation Patterns (CAPs)
- **CONCLUSIONS**

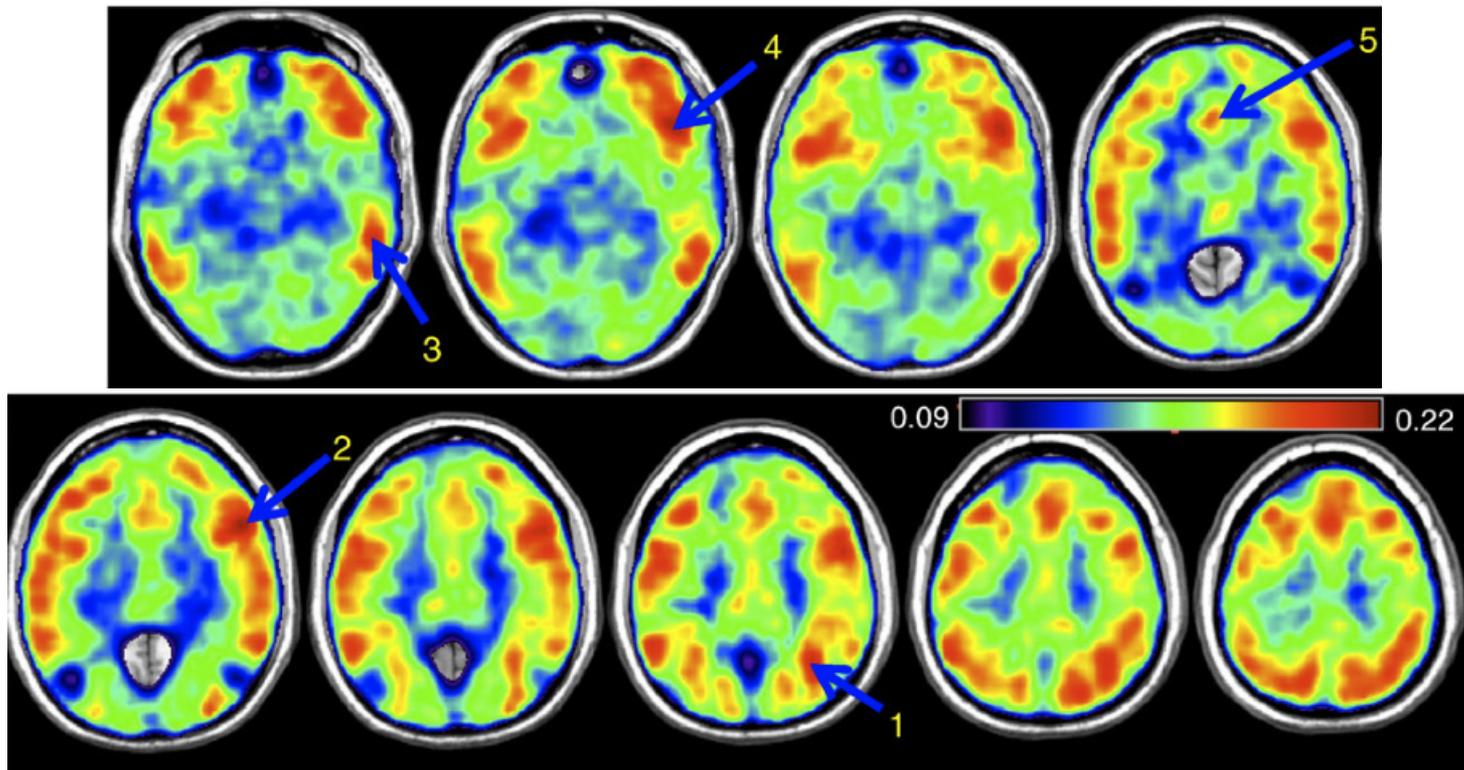


60 Minutes of Continuous Rest Data | TR = 1s

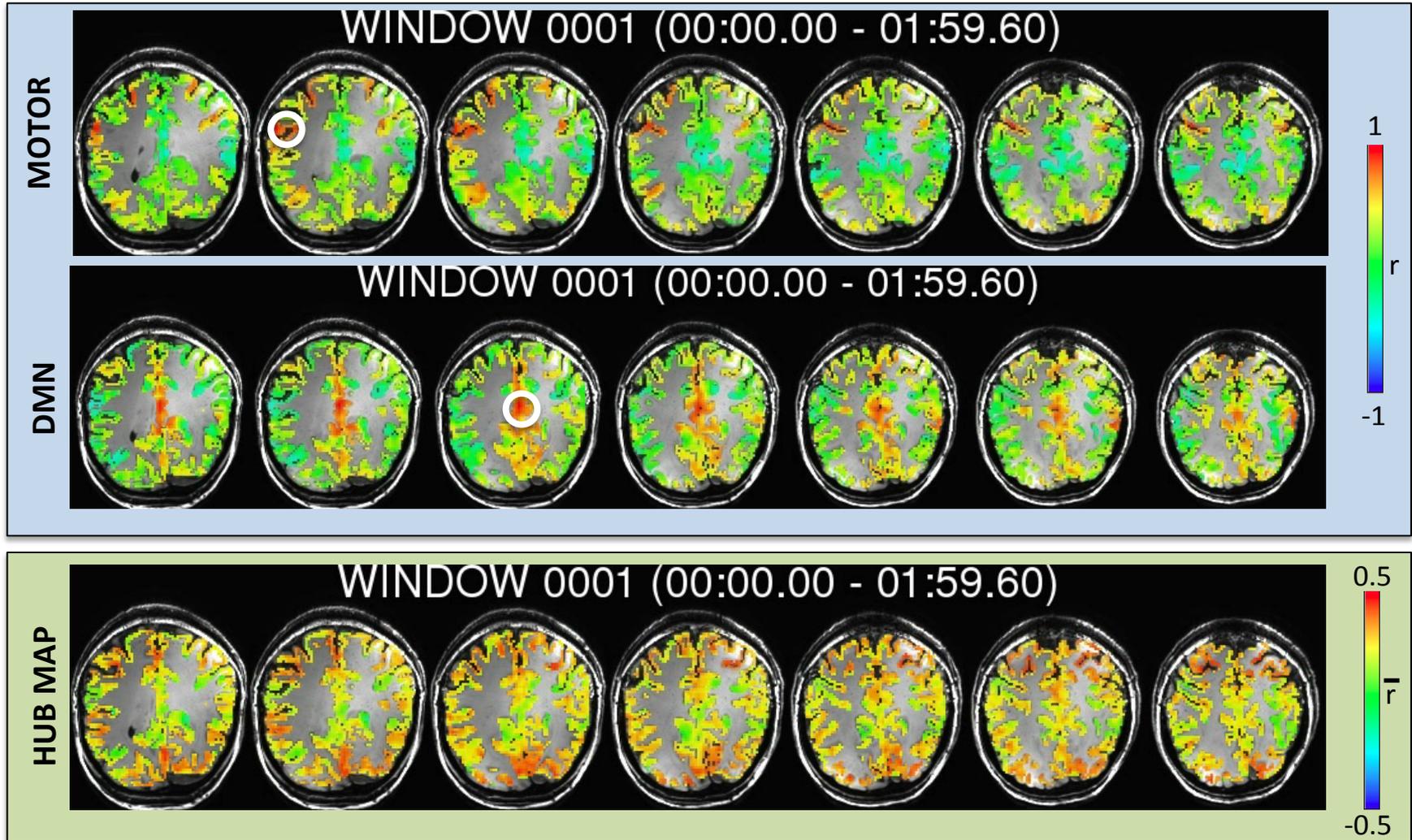
*“Most studies of resting-state functional connectivity using fMRI employ methods that assume temporal stationarity, such as correlation and data-driven decompositions computed across the duration of the scan. However, evidence from task-based fMRI studies and animal electrophysiology suggests that functional connectivity may exhibit changes within the time scale of seconds to minutes....”*



*“Most studies of resting-state functional connectivity using fMRI employ methods that assume temporal stationarity, such as correlation and data-driven decompositions computed across the duration of the scan. However, evidence from task-based fMRI studies and animal electrophysiology suggests that functional connectivity may exhibit changes within the time scale of seconds to minutes...”*

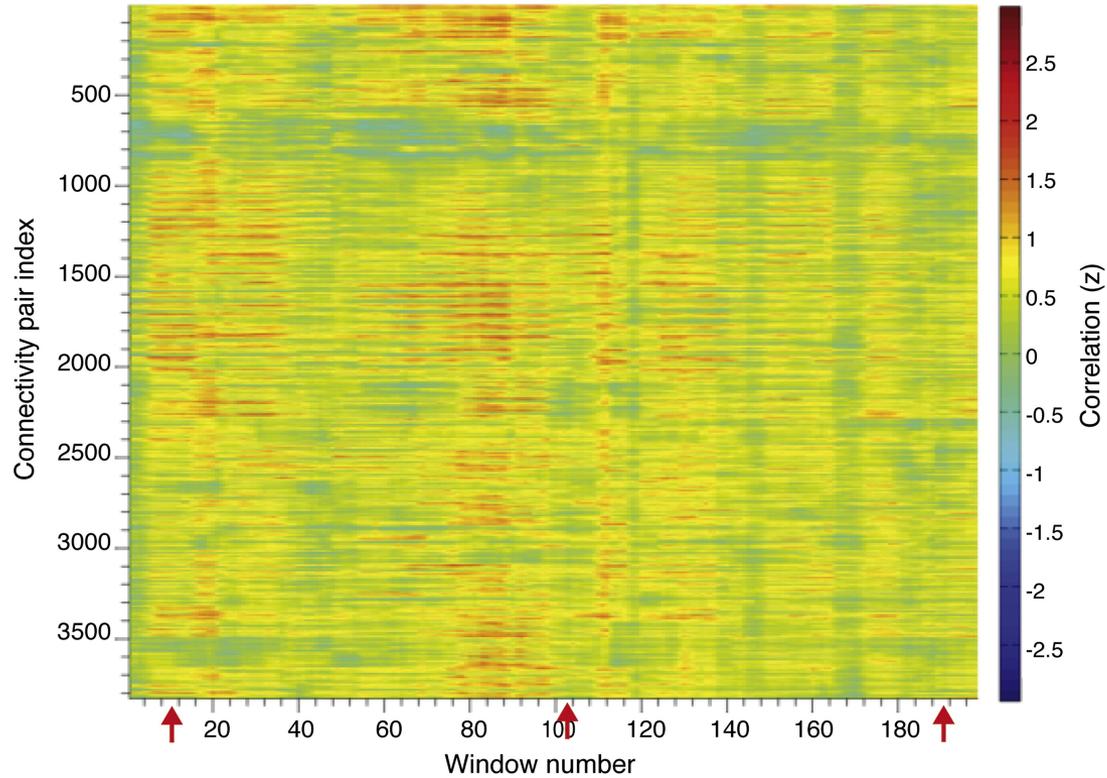


*“...Although it is unclear whether the observed coherence and phase variability can be attributed to residual noise or modulation of cognitive state, the present results illustrate that resting-state functional connectivity is not static, and it may prove valuable to consider measures of variability, in addition to average quantities, when characterizing resting state.”*

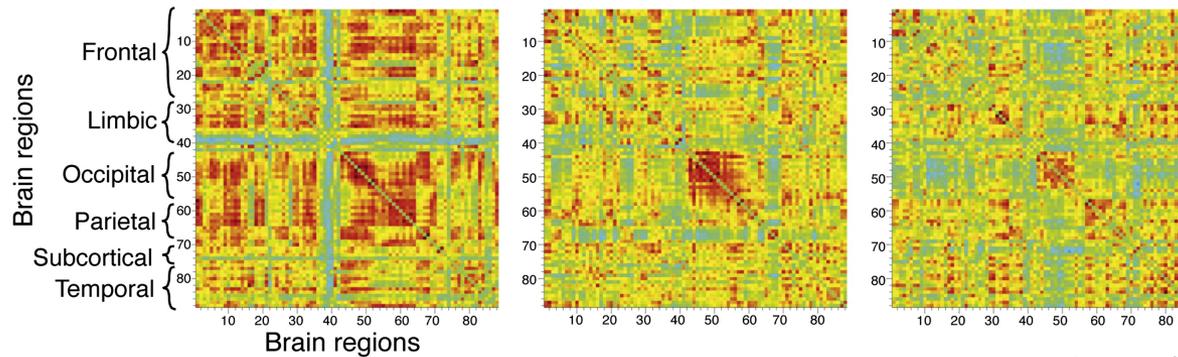


Window Size = 120 s | Window Step = 2s | Scan Length  $\approx$  55 mins | SBJ07

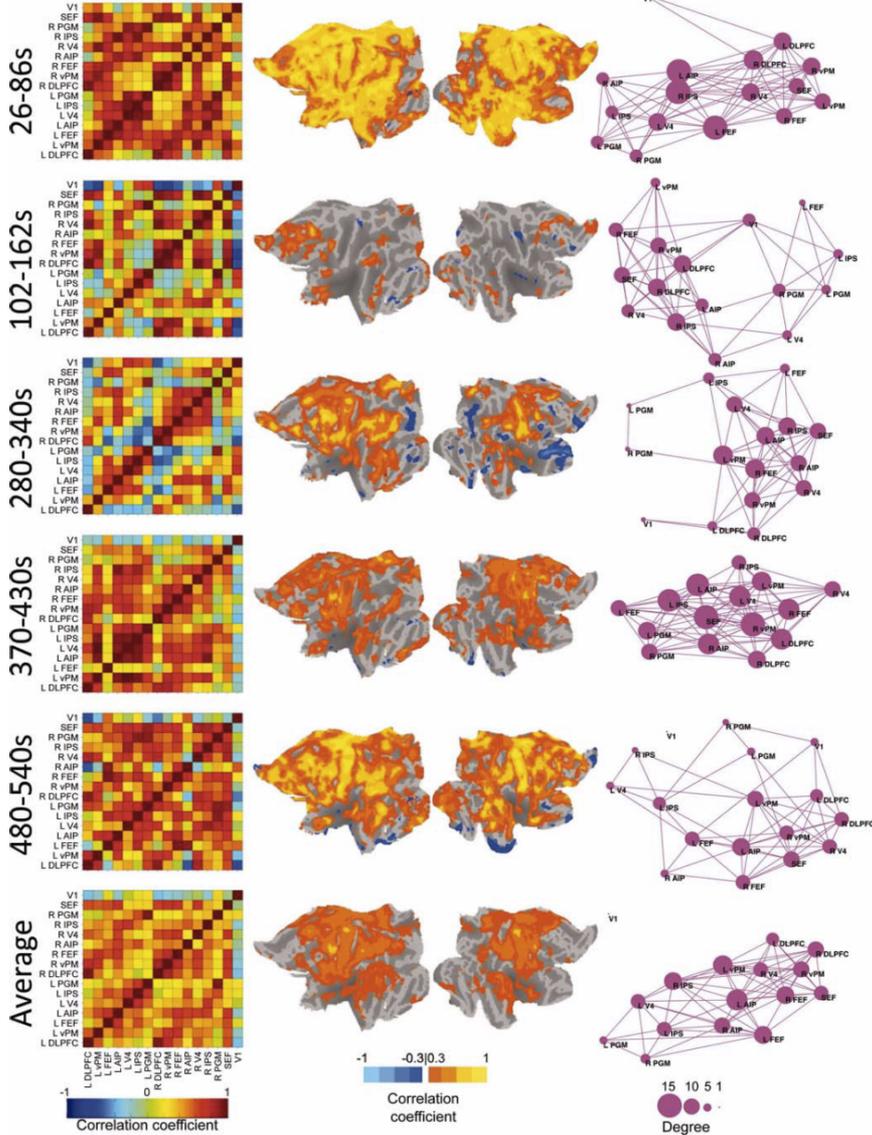
a) Dynamic FC



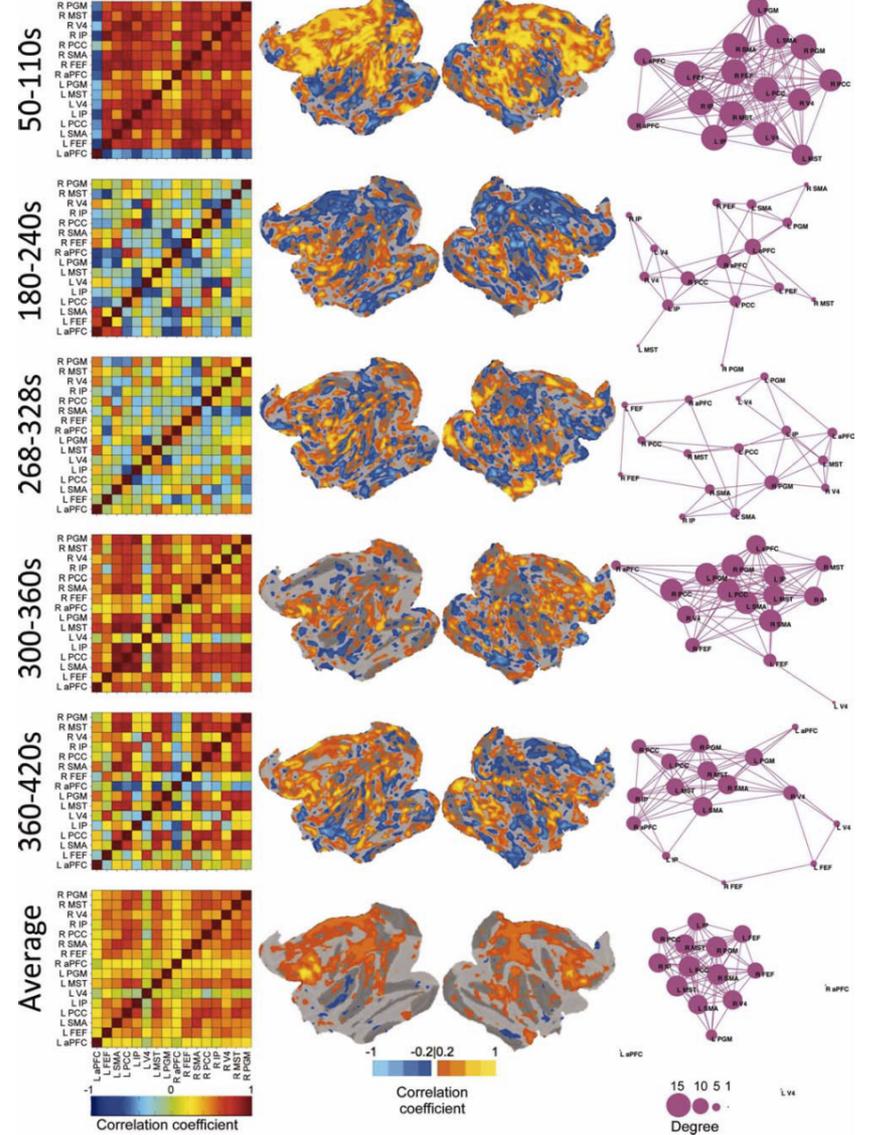
b) Example FC networks

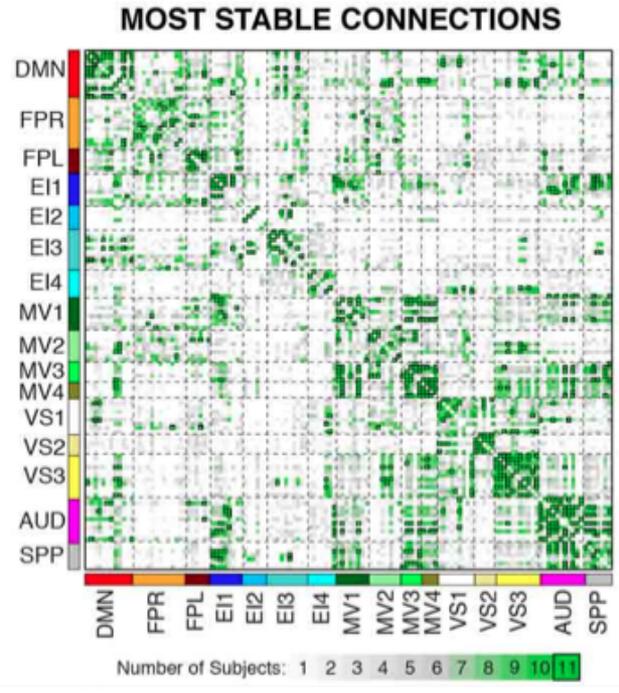
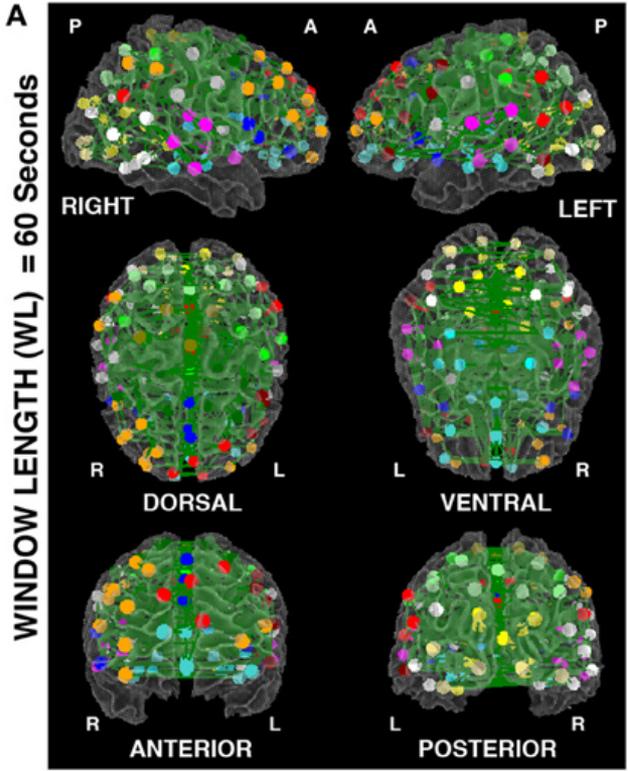


AWAKE HUMANS



ISOFLURANE-ANESTHESIZED MONKEY

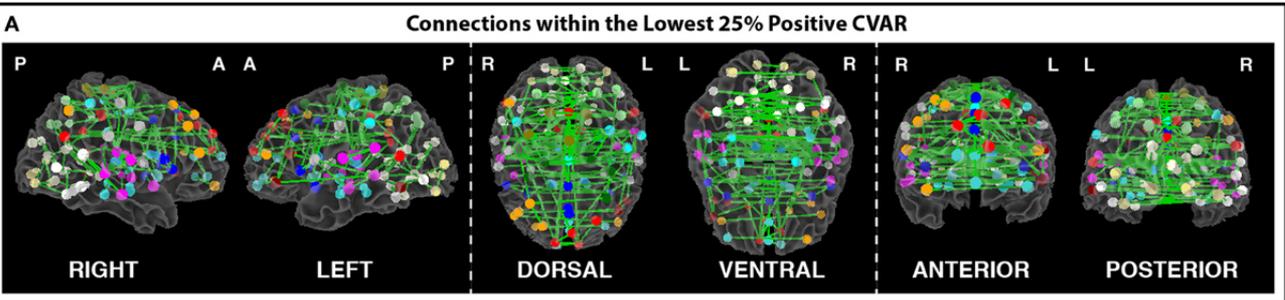


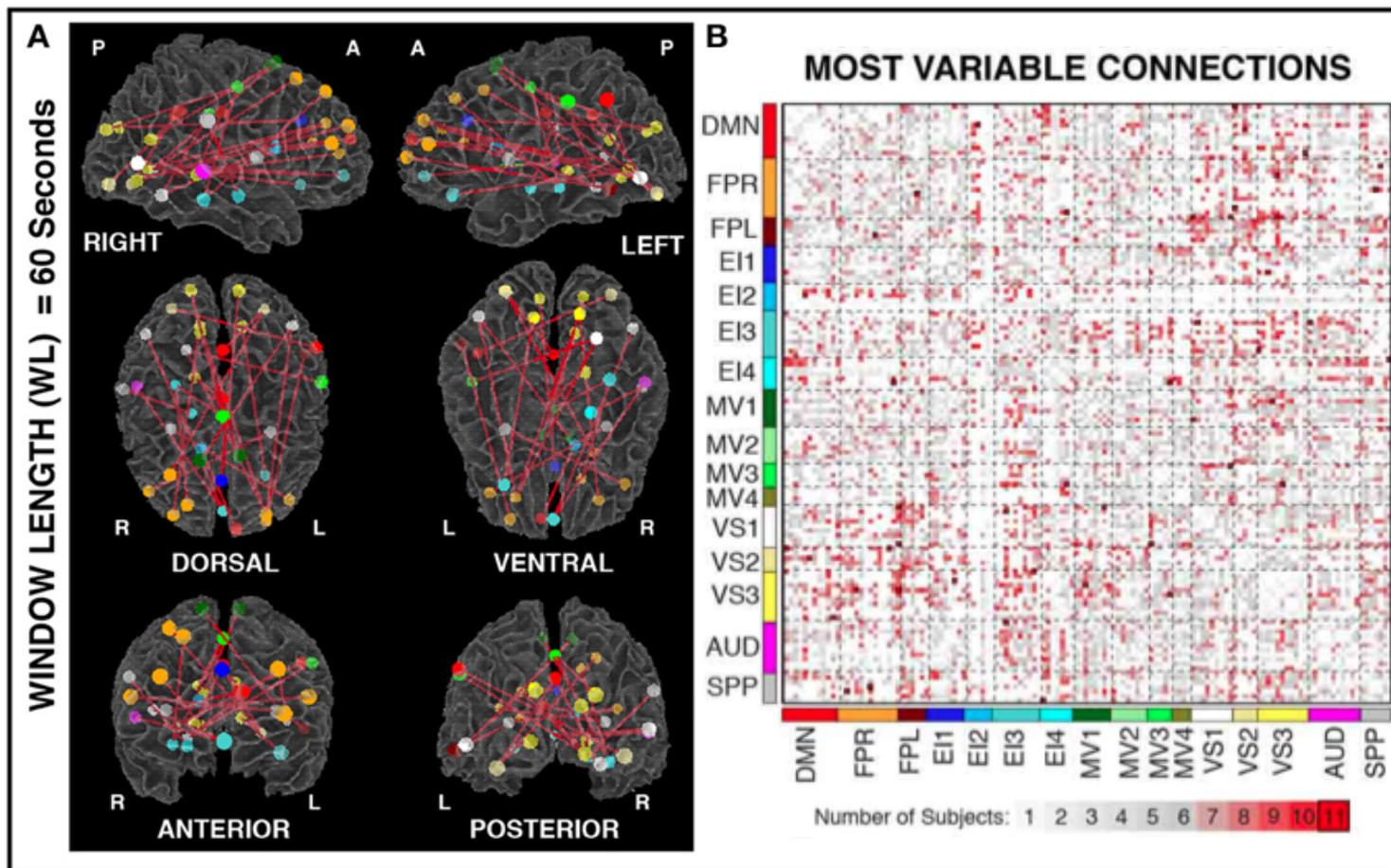


Mostly symmetric, inter-hemispheric connections between homologous right/left regions.

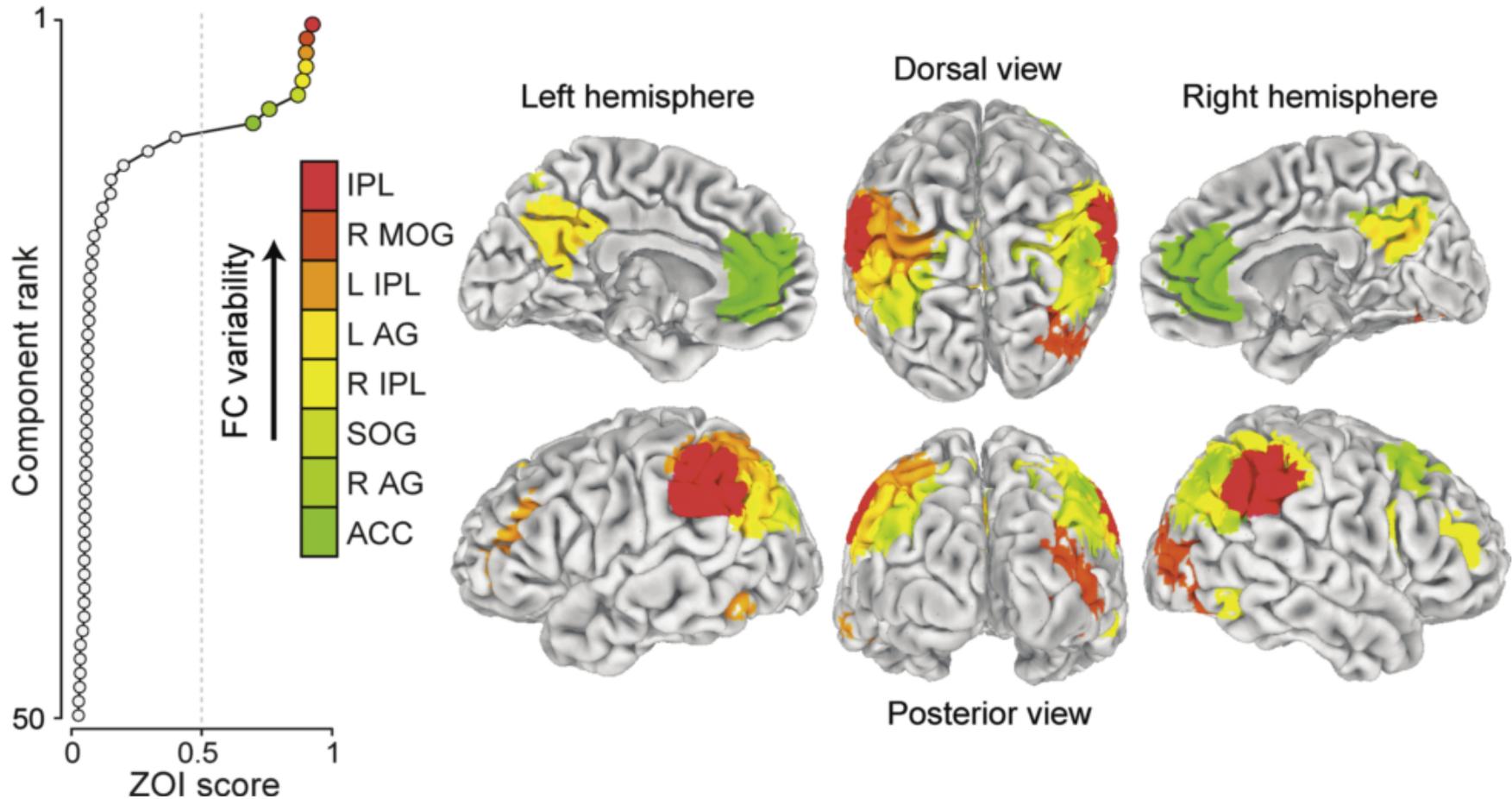
Only account for 32% of intra-network connections → Networks are flexible

Unimodal sensory-motor networks (VIS, AUD and MV) seems to be among the most stable.



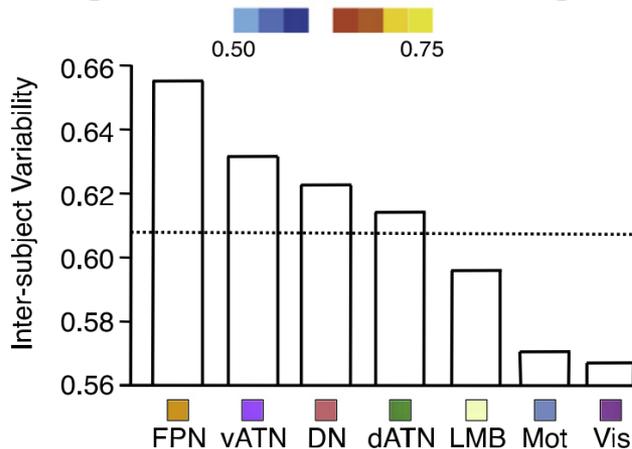
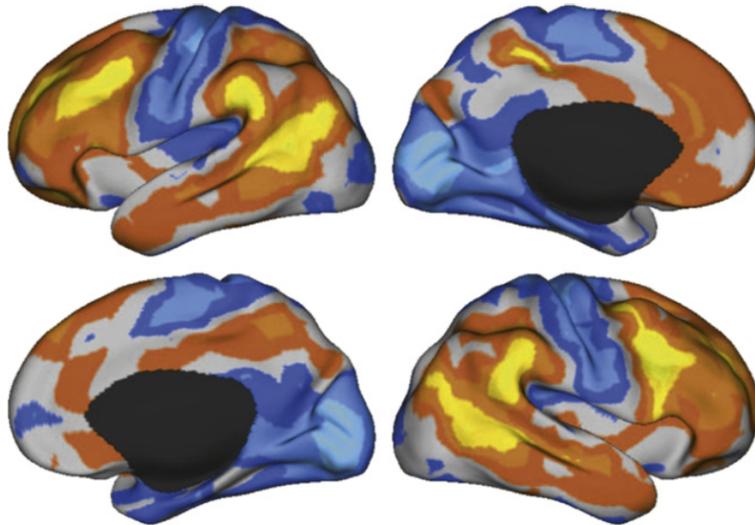


Most Variable Connections correspond primarily inter-network, inter-hemispheric connections involving the fronto-parietal network and occipital regions. Also some DMN regions.



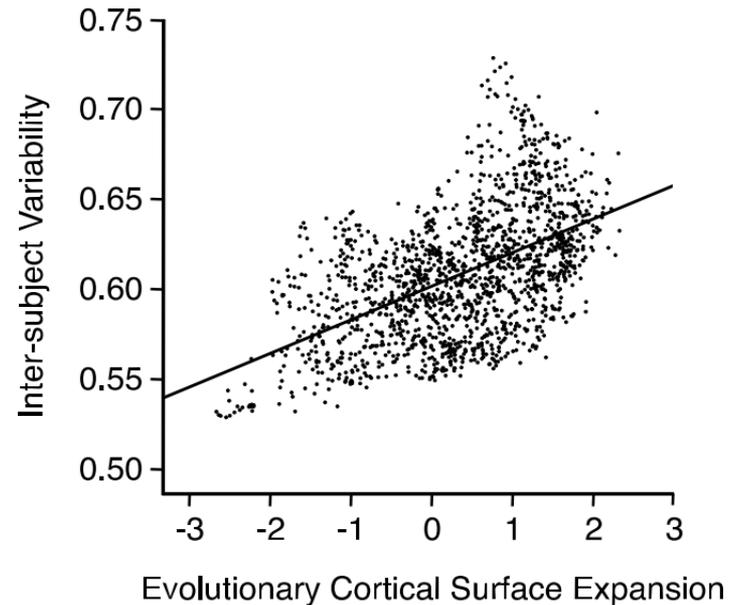
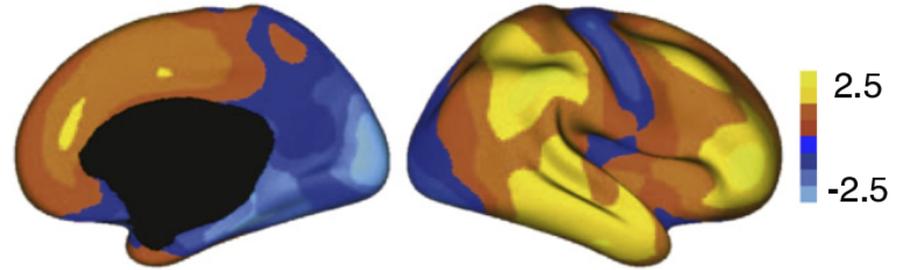
**ZONE OF INSTABILITY:** Set of Intrinsic Connectivity Networks with the most variable FC based on approx. 6 min long rest scans acquired on a group of 405 young adults and using a window length of 44 seconds.

Inter-subject Variability in FC

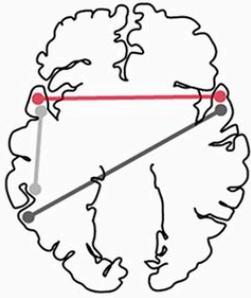


Higher inter-subject variability in FC in heteromodal association cortex and lower variability in unimodal cortex.

A Evolutionary Cortical Surface Expansion



Functional Connectivity variability is highly correlated with evolutionary cortical surface expansion.

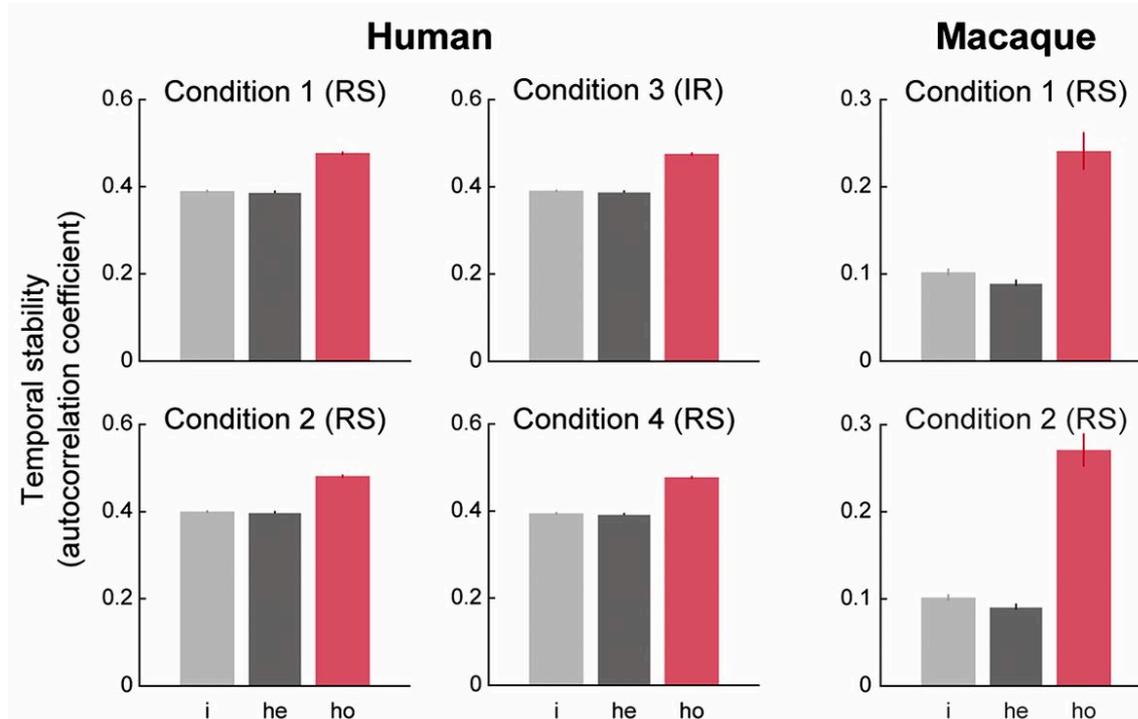


Connection type:  
 intrahemispheric (i)  
 heterotopic (he)  
 homotopic (ho)

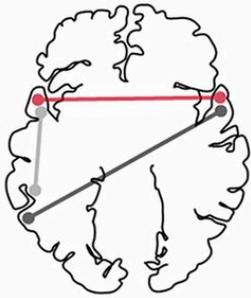
Ho: Interhemispheric connections between homologous rois  
 He: Interhemispheric connections between non-homologous rois  
 I: Intrahemispheric connections.

Human Data: 2 Conditions Rest | Induced Negative Rumination  
 Macaque Data: 1 Condition Light Anesthesia

Across conditions & species, Homotopic FC is the most stable of all 3 types of connections.



WL=60s | Equivalent results for WL=120s & WL=30s

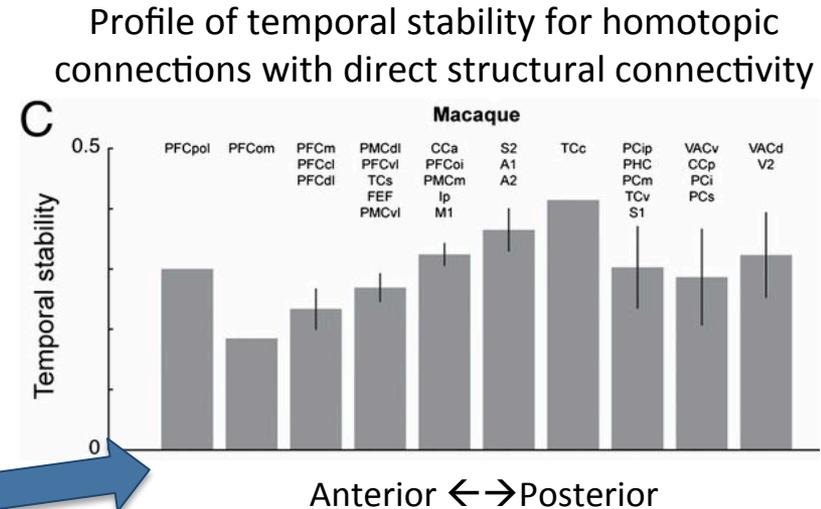
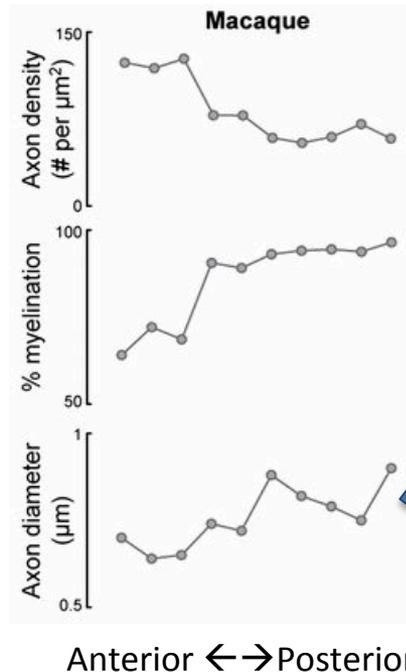
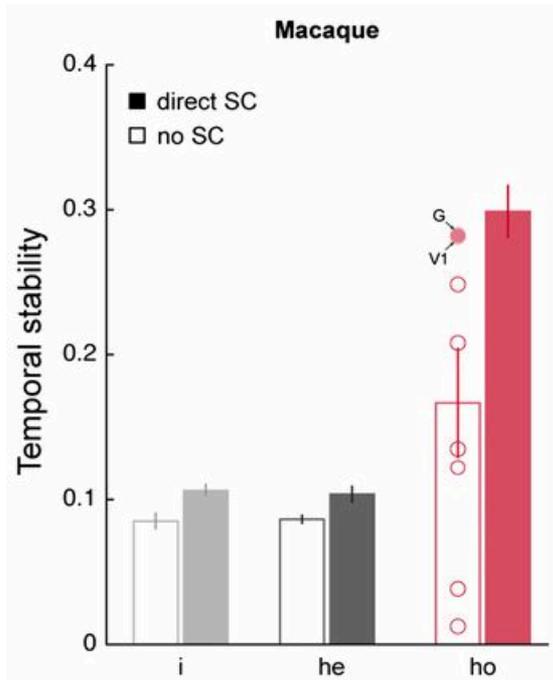


Connection type:  
 intrahemispheric (i)  
 heterotopic (he)  
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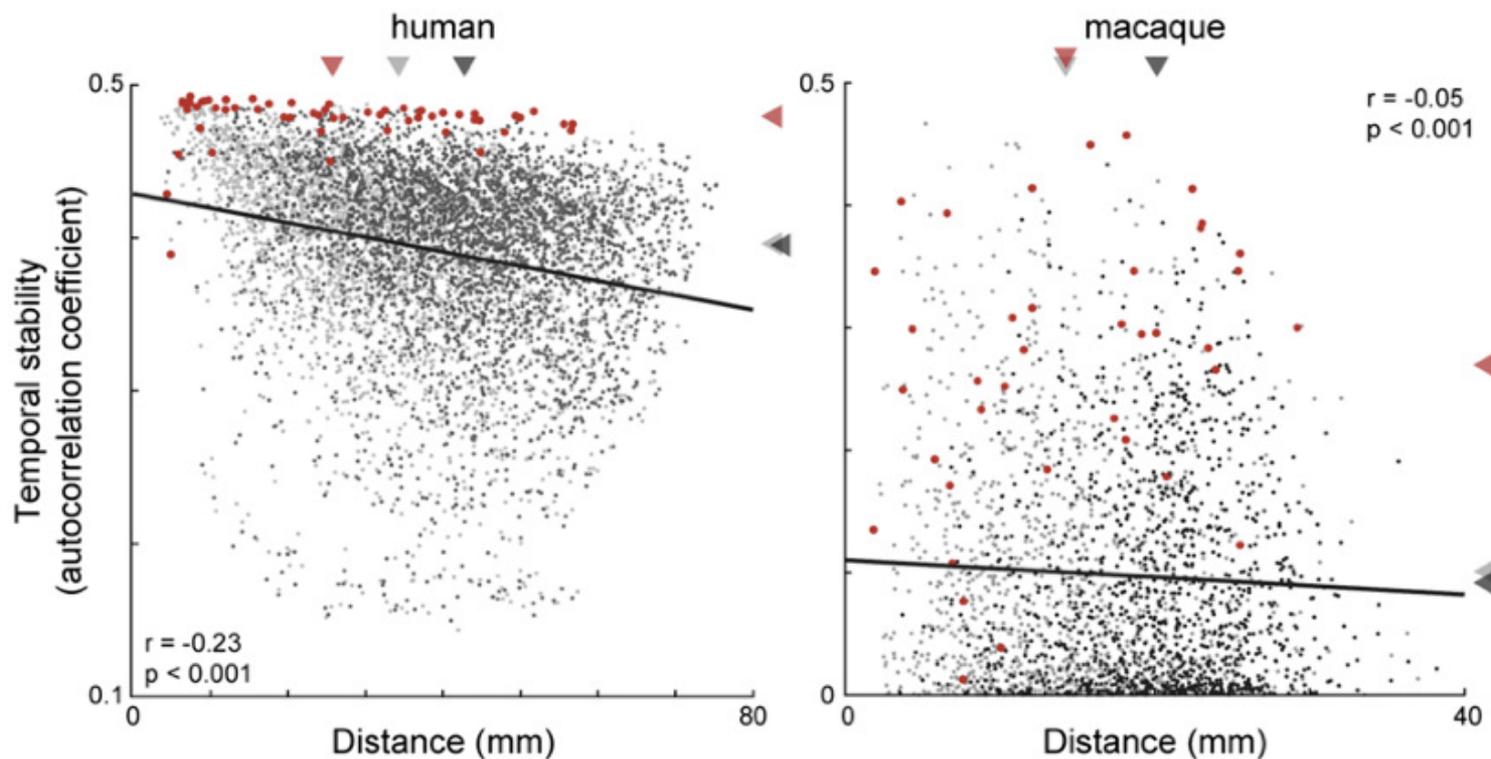
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 I: Intrahemispheric connections.

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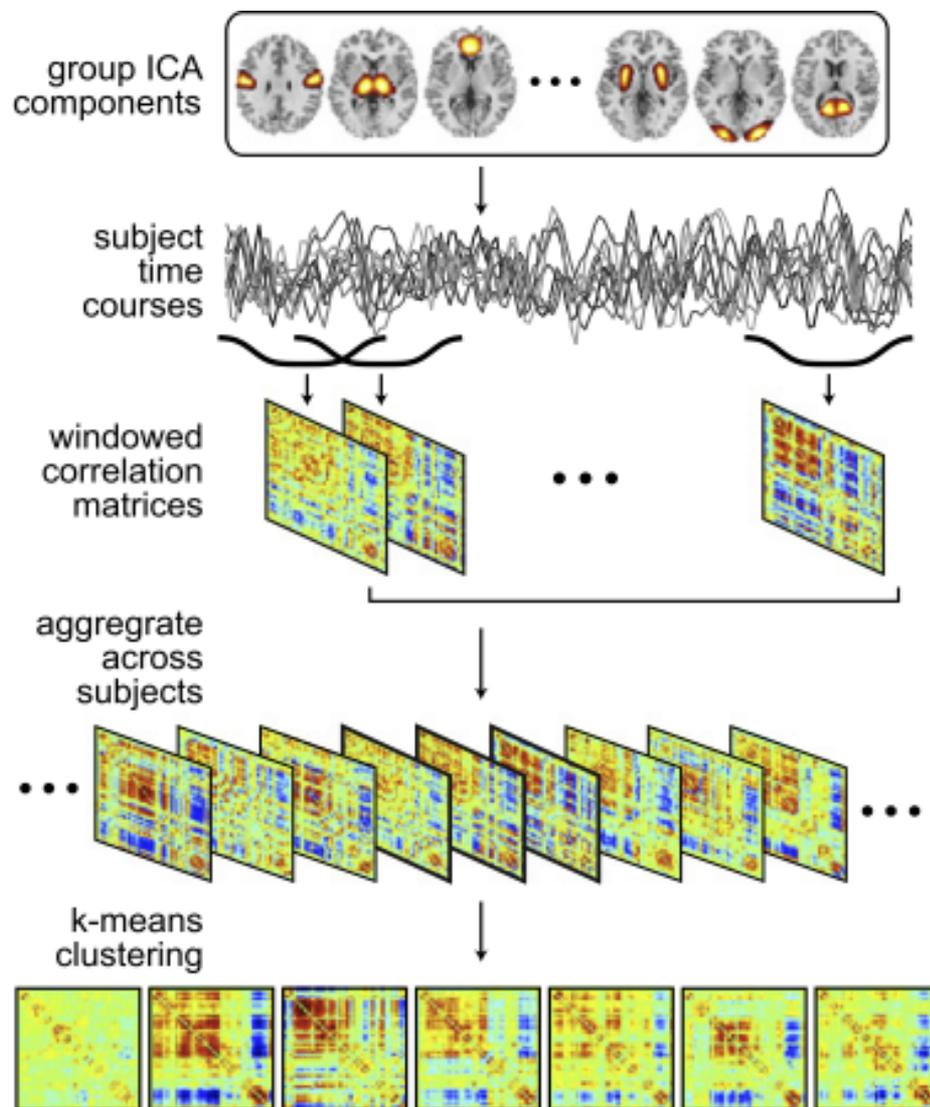
**Temporal stability of homotopic FC is facilitated by direct anatomical projections and their conduction characteristics**

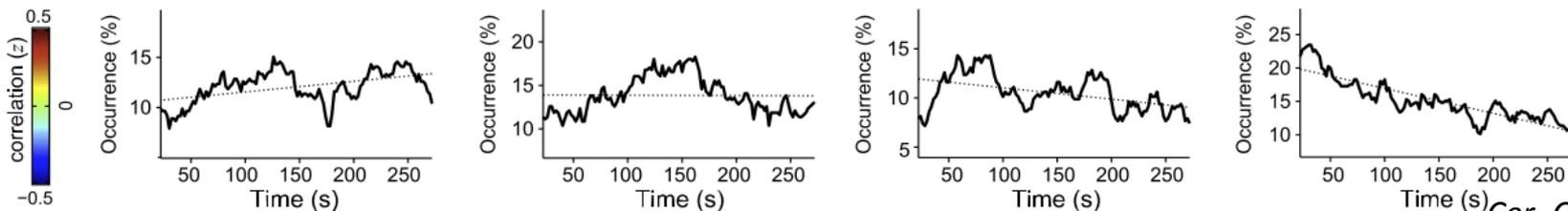
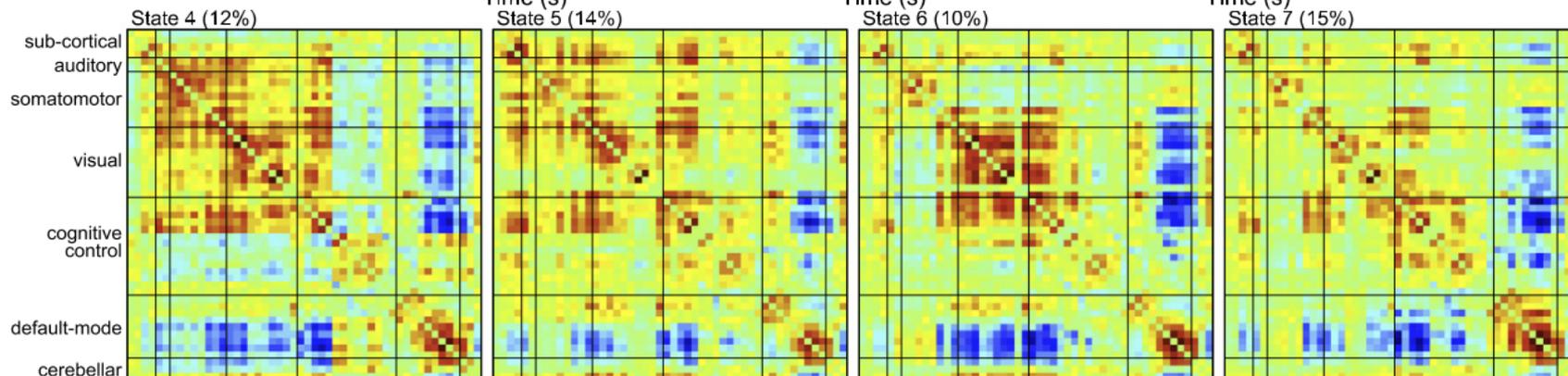
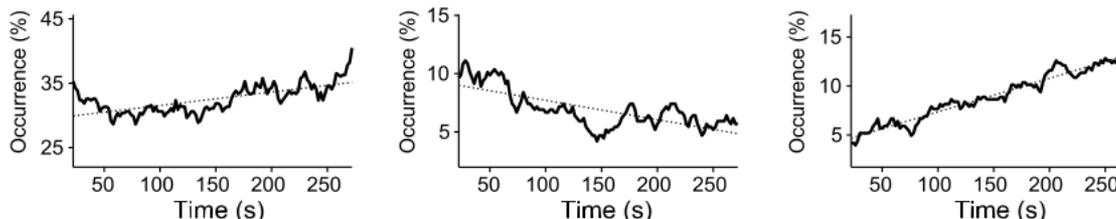
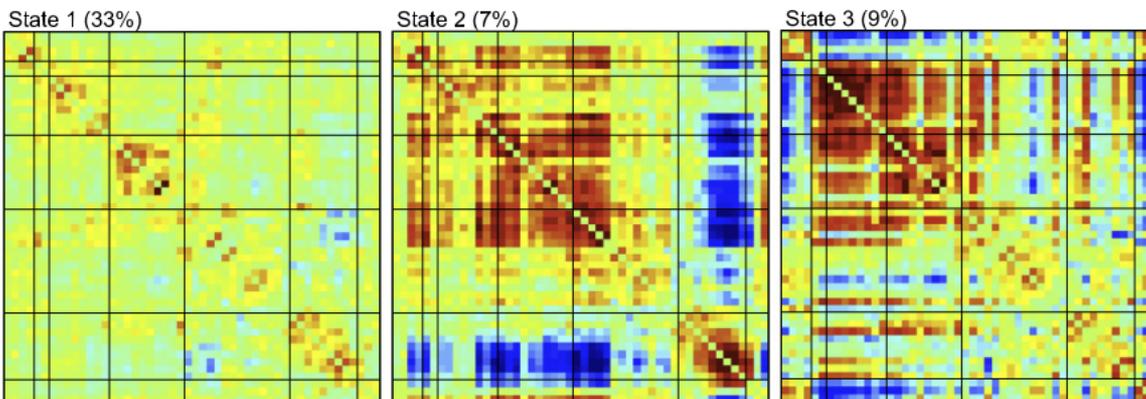


## (5) FC Stability independent of distance



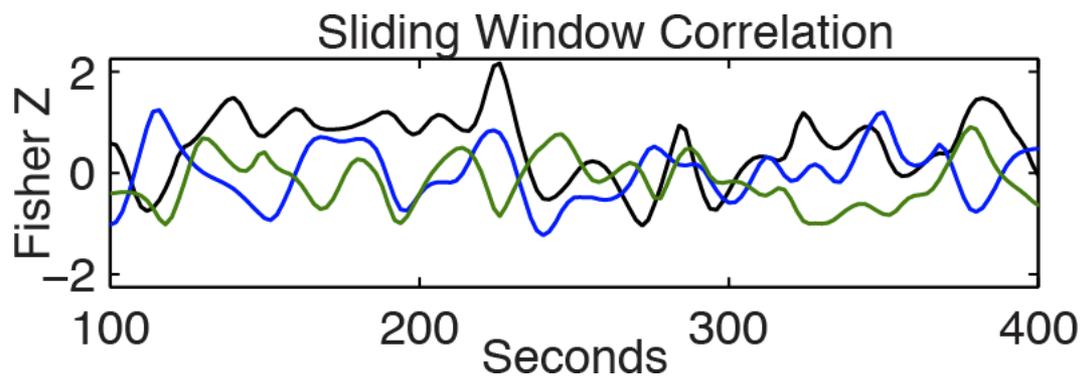
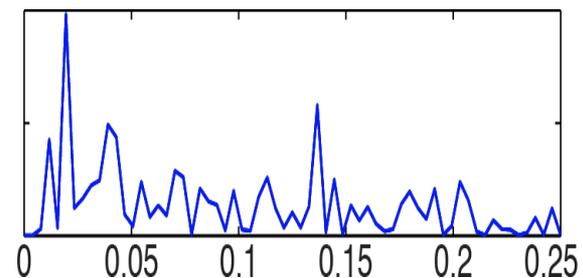
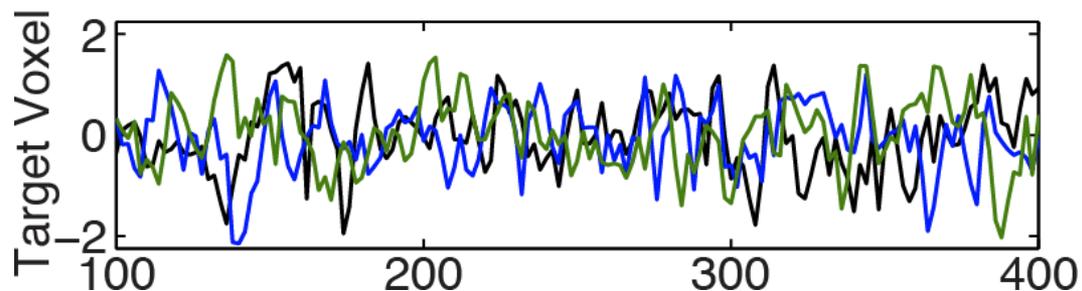
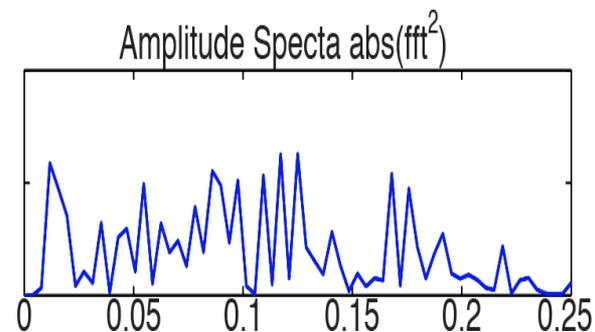
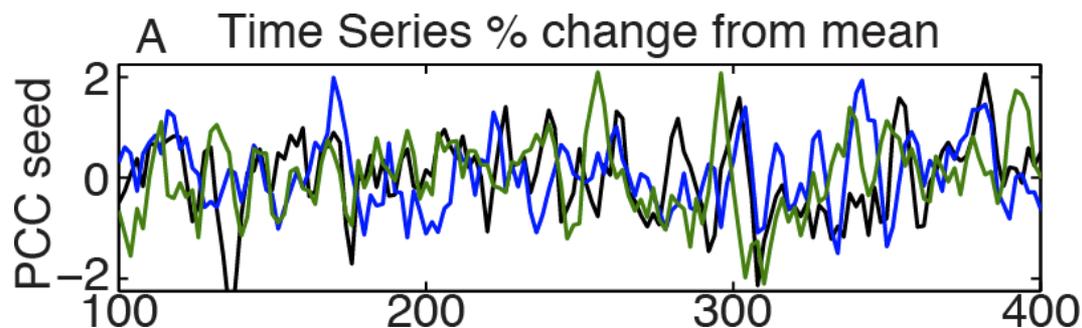
**FUNCTIONAL CONNECTIVITY STATES:** a series of re-occurring short-term (in the order of seconds) whole-brain connectivity patterns that are common across subjects.





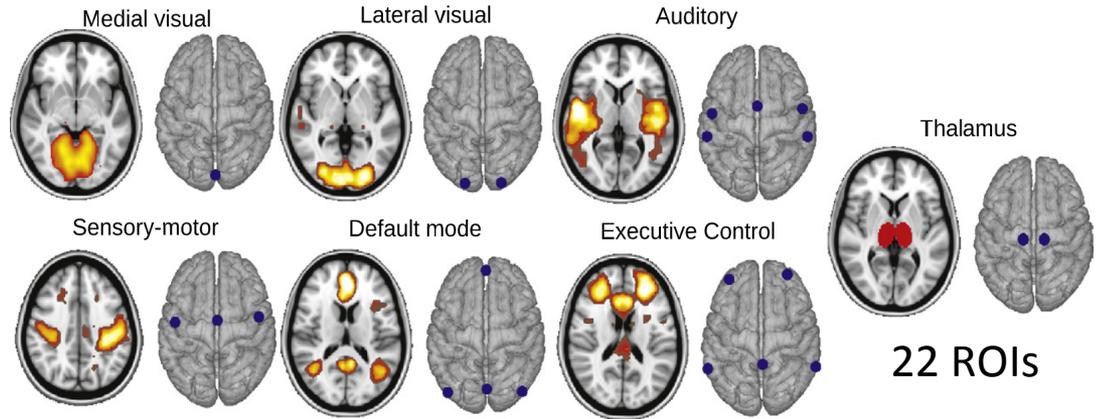
- ❖ FC exhibit a rich dynamic behavior at the scale of minutes to seconds.
- ❖ Present both in awake humans, as well as, anesthetized macaques.
- ❖ Observed short-term FC patterns can deviate significantly from average/stationary FC patterns.
- ❖ FC Dynamics have well defined spatial patterns:
  - Interhemispheric Homotopic Connections are among the most stable.
  - Heterotopic Connections are among the most variable.
- ❖ Spatial distribution of FC Dynamics overlap with:
  - Spatial maps of Between-Subject Long Term FC Stability.
  - Spatial maps of evolutionary cortical expansion.
- ❖ There are reproducible re-occurring patterns of whole brain connectivity common across subjects, commonly referred to as “Functional Connectivity States”.
  - Depart substantially from average connectivity patterns (networks break down).
  - Have the potential to be biologically/cognitively meaningful.

**RELATIONSHIP TO  
COGNITIVE/MENTAL STATES  
&  
PRELIMINARY CLINICAL  
APPLICATIONS**

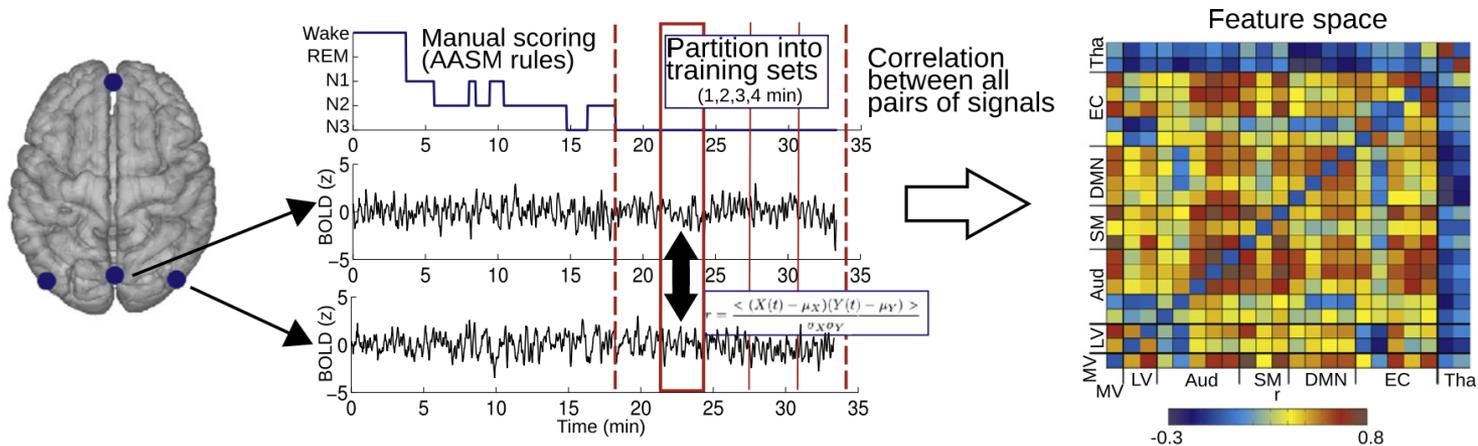


Regardless of whether or not there are neuronal interactions, two random time-series can show sliding window correlation dynamics.

- Concurrent BOLD fMRI and EEG Recordings.
- Approx. 50 min long scans.
- Manual Sleep Staging based on EEG/AASM Criteria.
- WL = 60 s – 4 minutes

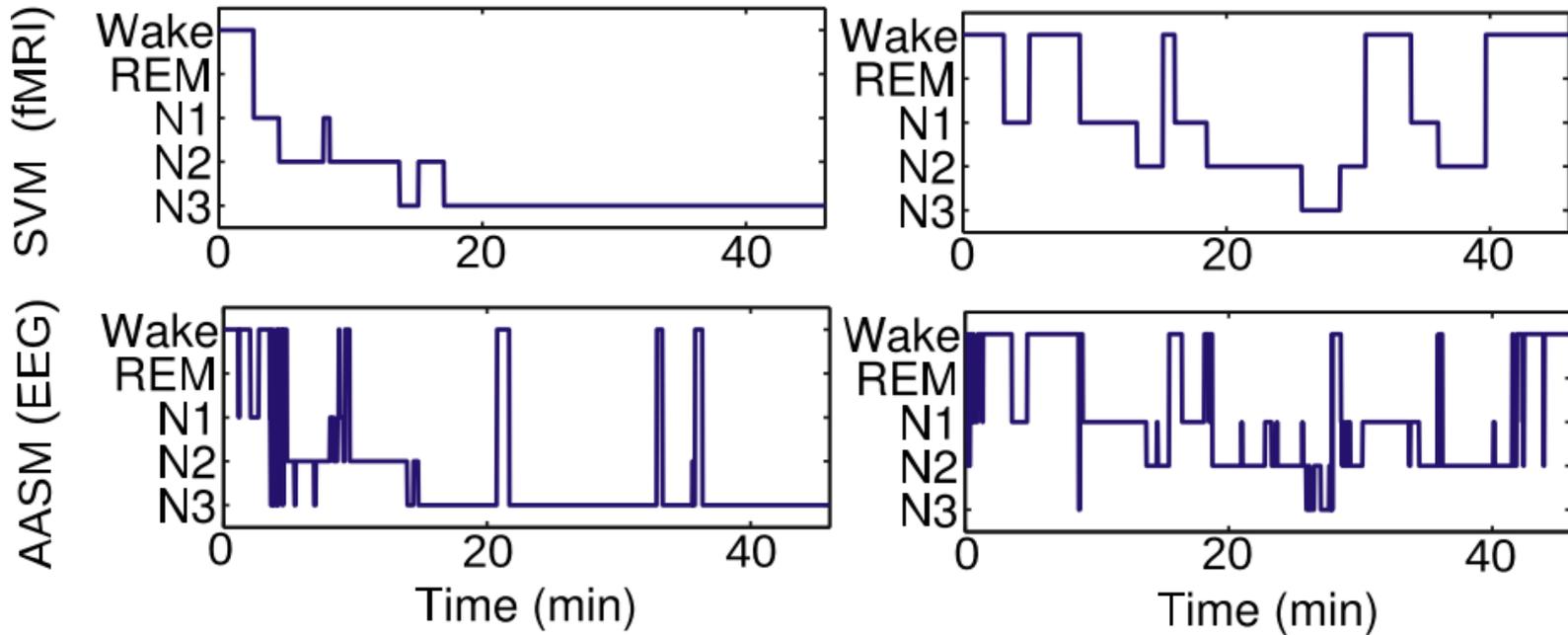


Training Phase



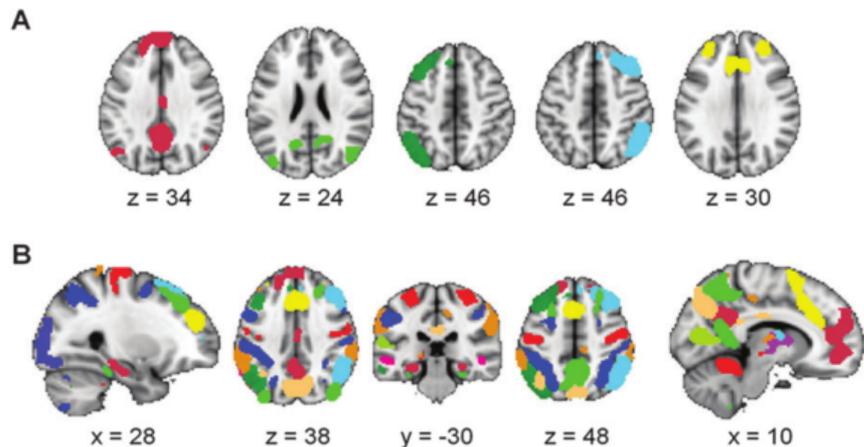
Algorithm: Multi-level Support Vector Machine

## Test set #1 (wake &amp; sleep)

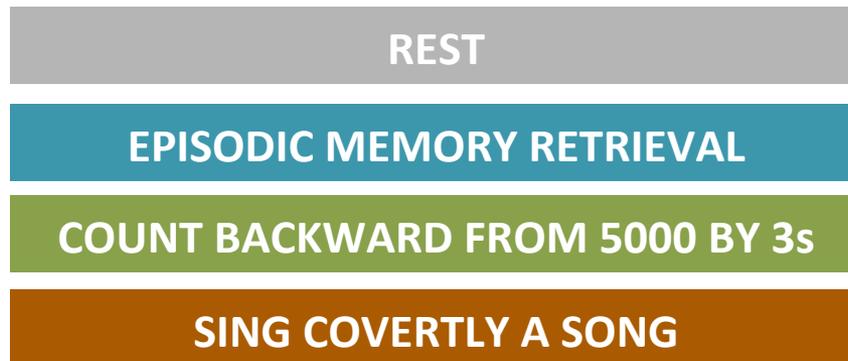


80% Accuracy for WL = 2 mins and above

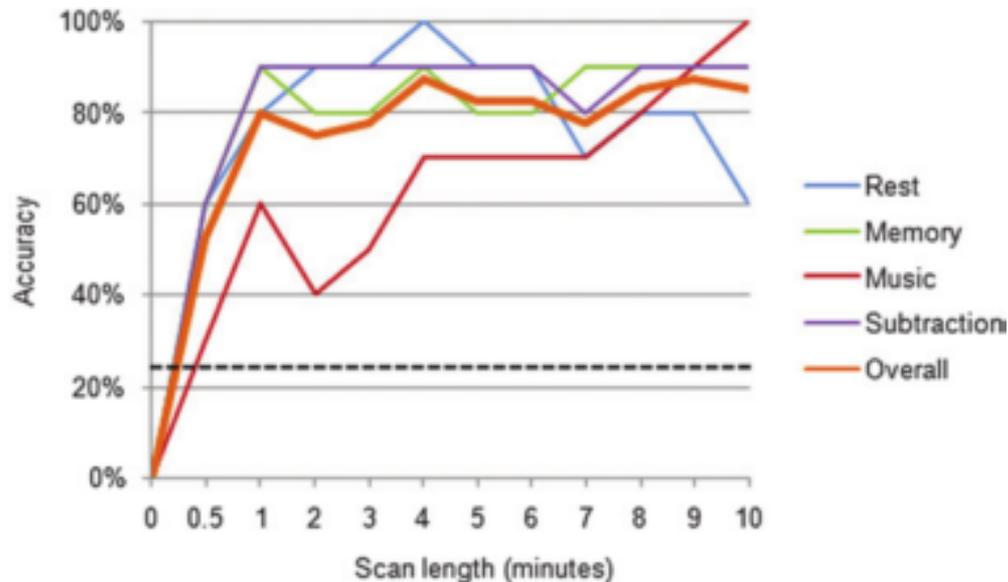
90 Functionally Defined ROIs

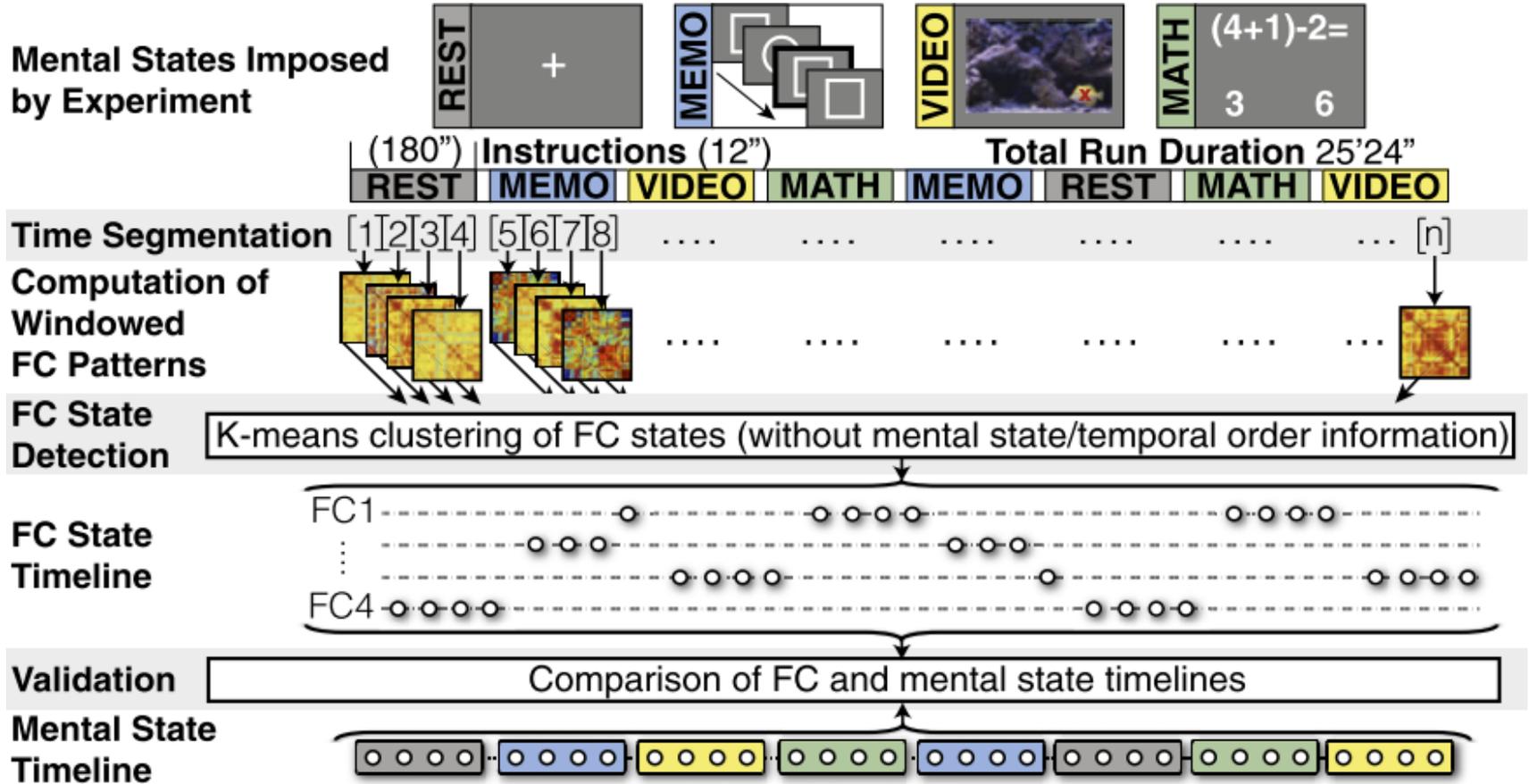


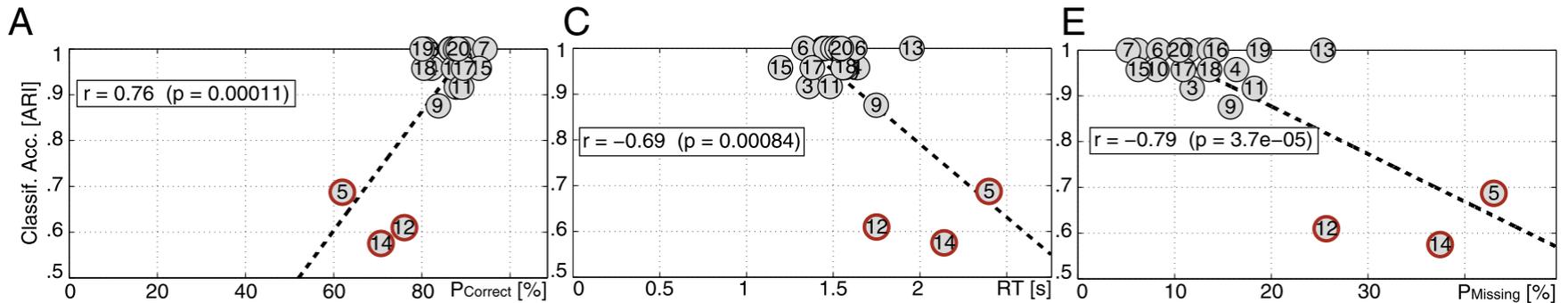
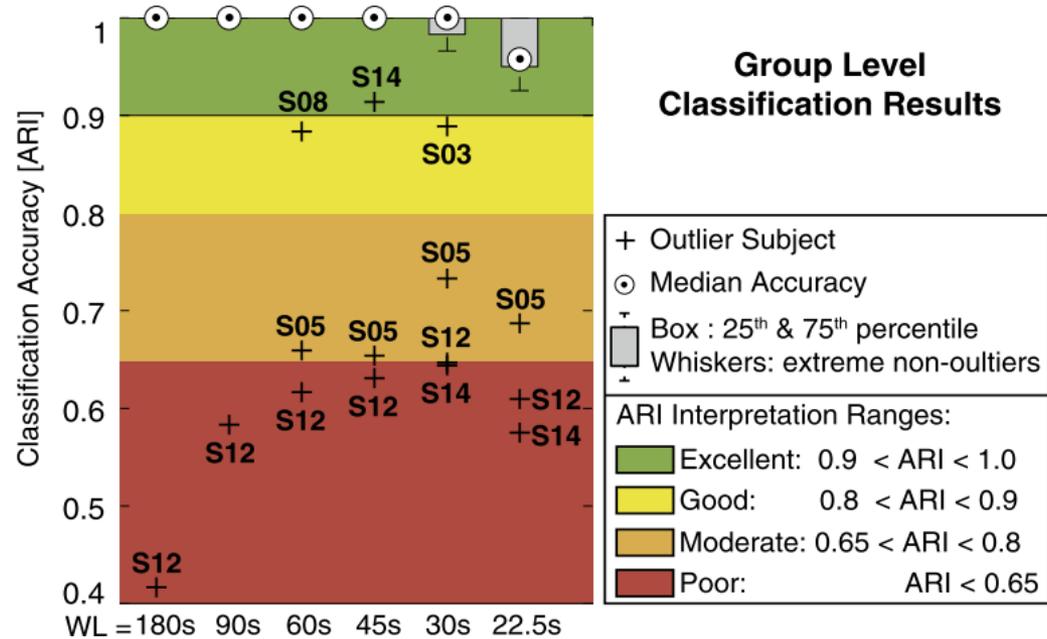
Four different 10 min scans as subject engage in different self-driven mental states.



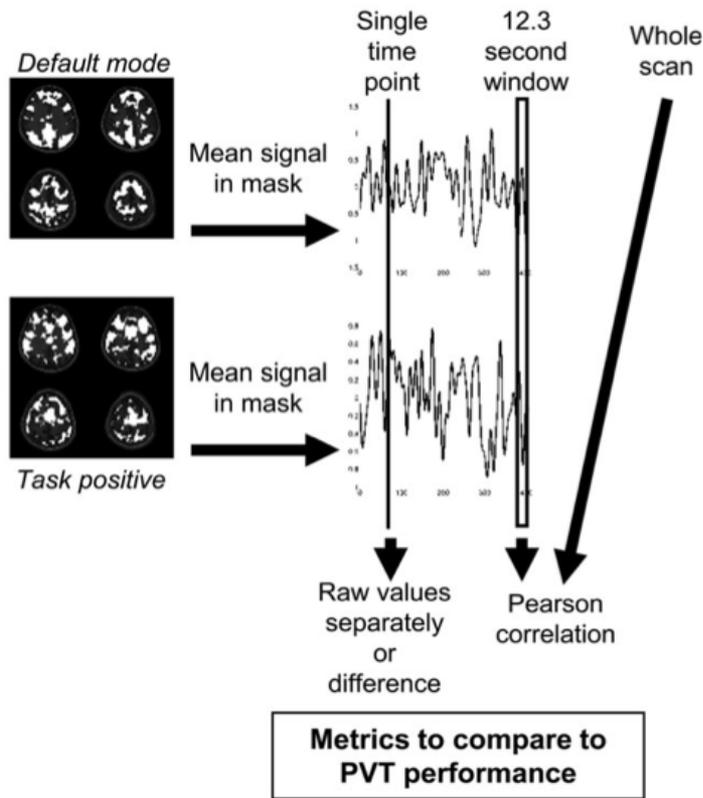
Algorithm: Pre-selection of Connections of Interest + Maximum Matrix Similarity to Training Dataset.





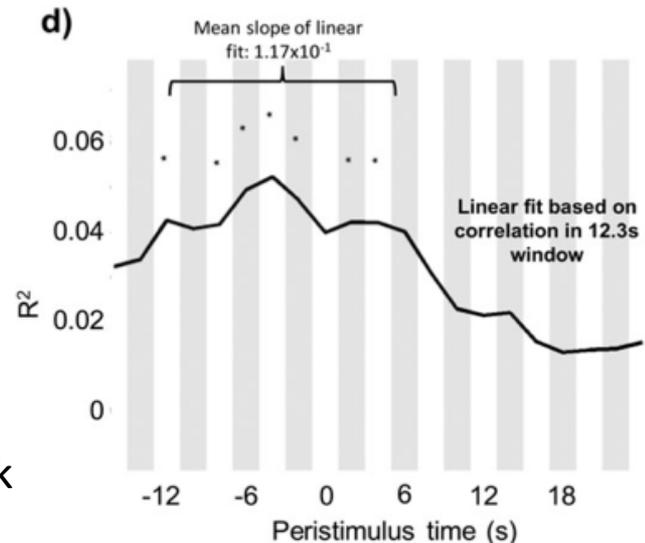
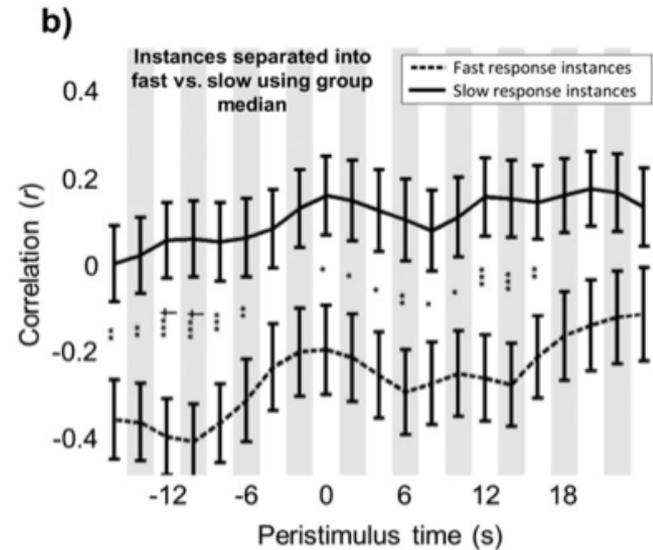


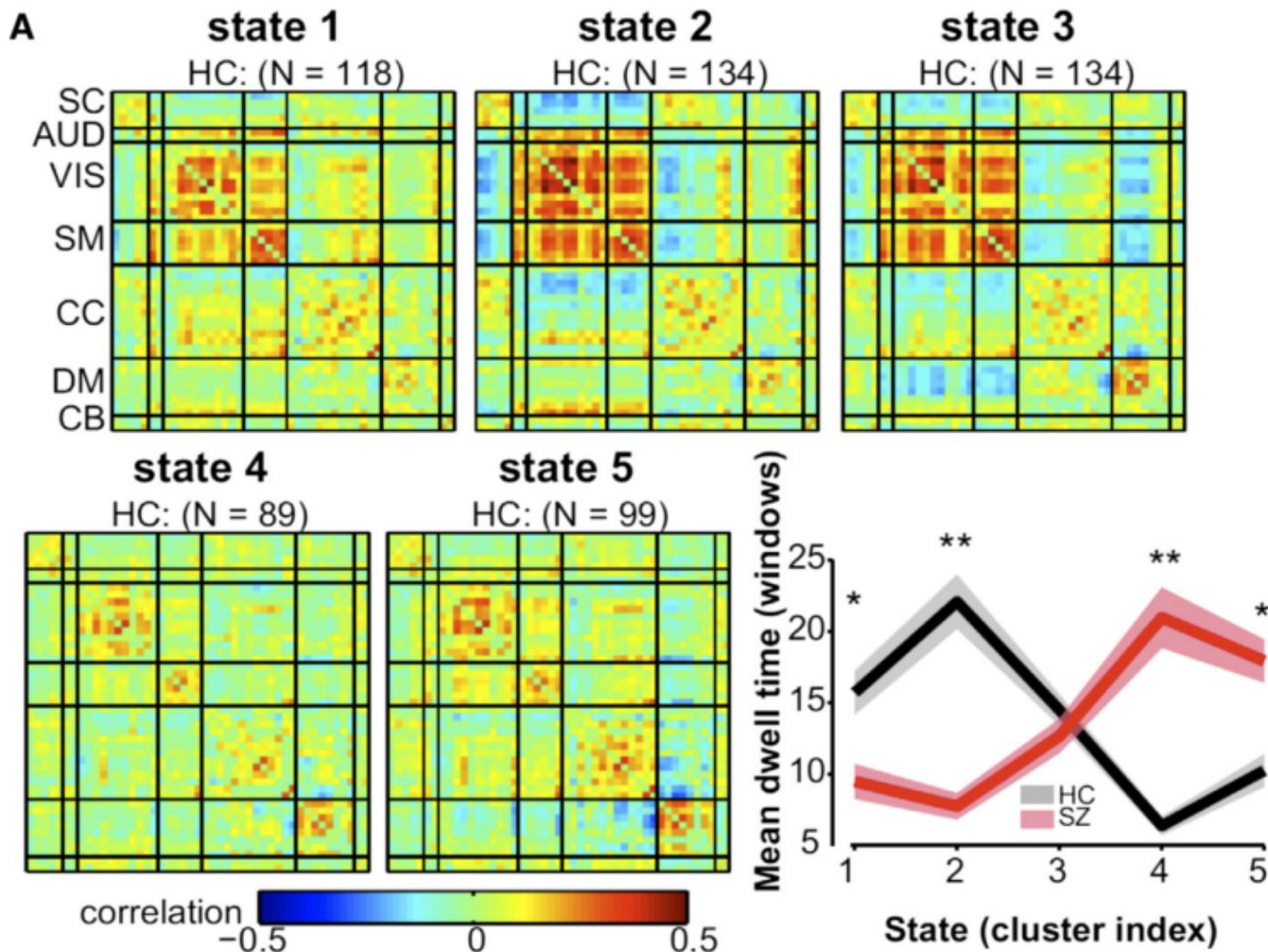
Examined the relationship between a psychomotor vigilance task and the interacting default mode and task positive networks.



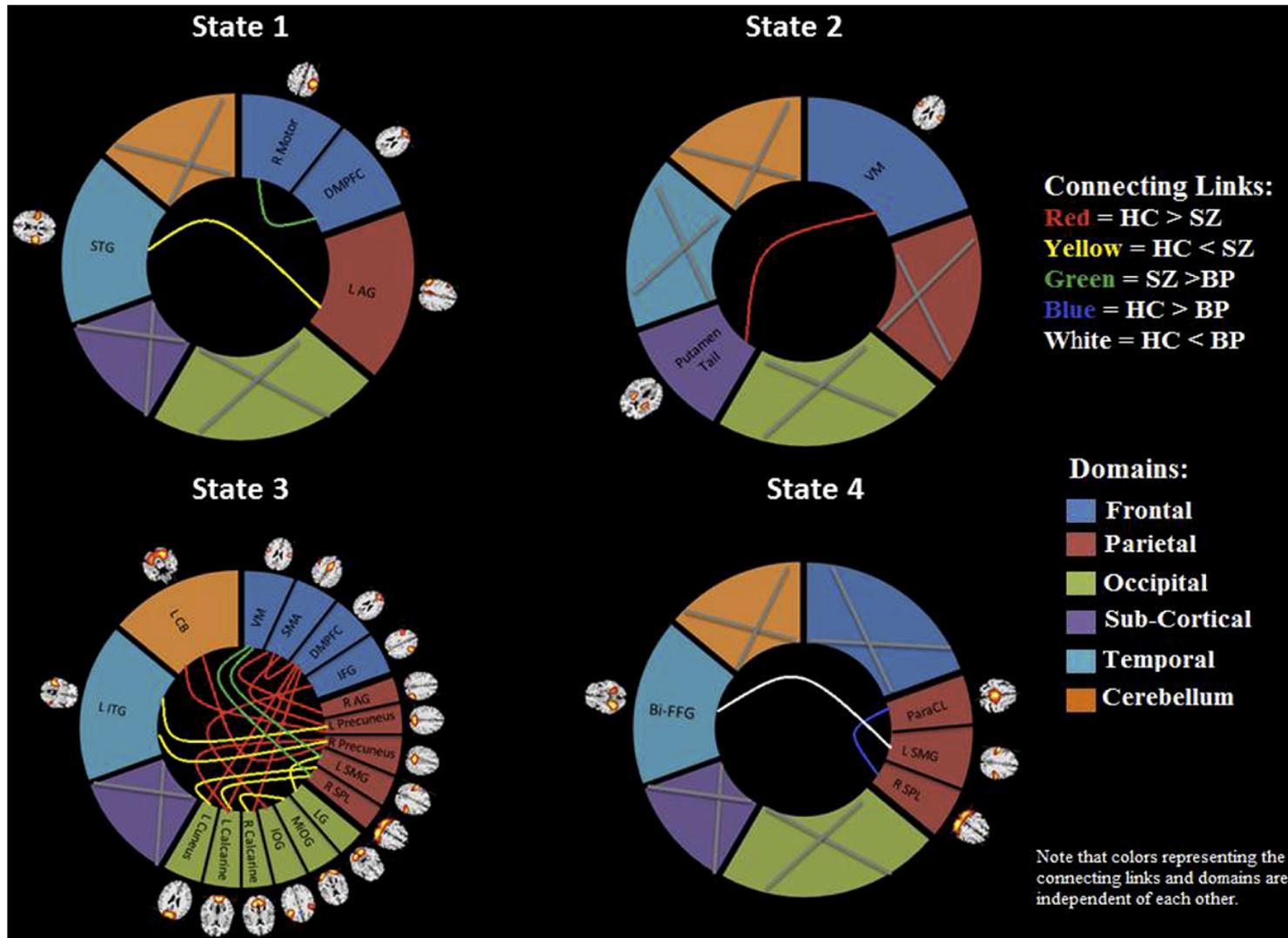
TR = 300ms

In most cases, more anti-correlation between network was significantly related to faster performance.





Dynamic states in a large ( $n > 300$ ) data set of schizophrenia patients and controls in which the patients are spending significantly more time in the relatively less connected state 4.

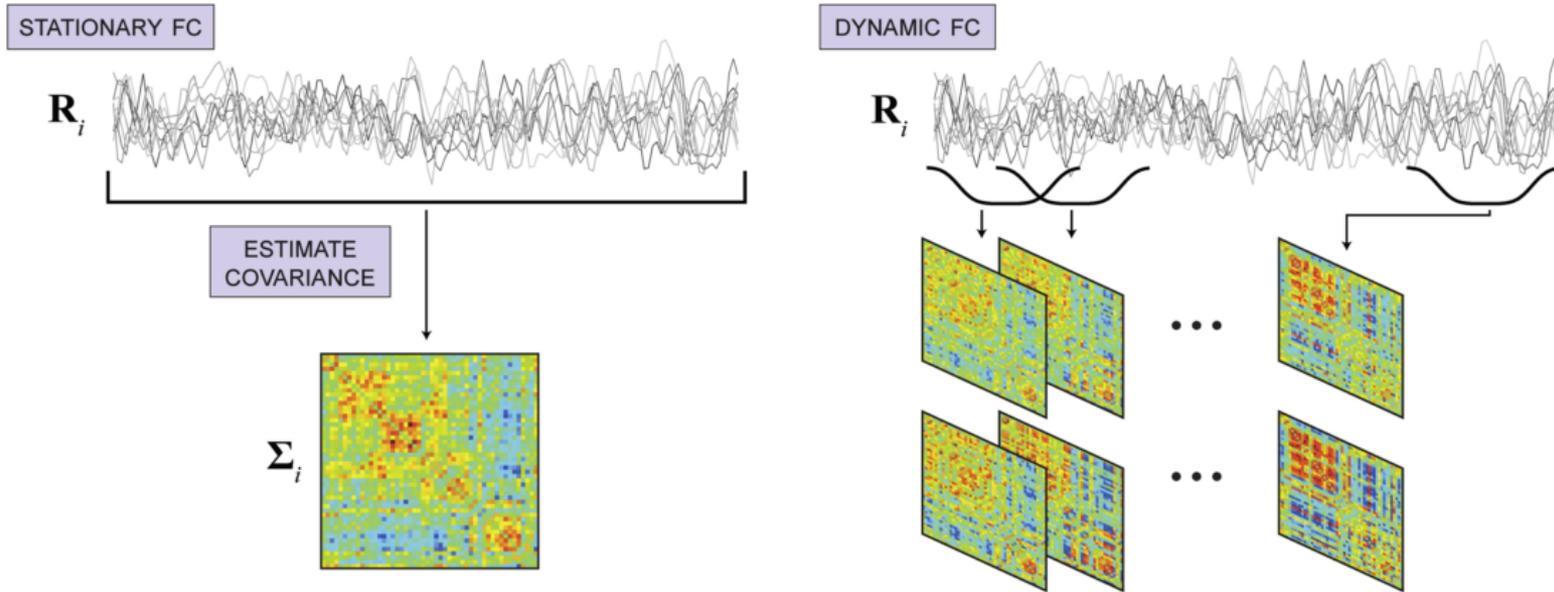


“Specific states differentiate schizophrenia, bipolar, and healthy controls... and that most of these are tied to a single state in this case.” *Rashid et al. Frontiers in Neuroscience, 2014*

- ❖ **Dynamic changes in FC at the scale of seconds to minutes can be used to:**
  - Reliably perform automatic sleep staging at the single subject level.
  - Discriminate between externally imposed mental states at the single subject level.
  - Predict Task performance on an individual basis.
  
- ❖ **Huge Diversity of Experimental and Analytical Methods:**
  - Differences in Acquisition: scan durations / TRs / window lengths
  - Differences in Pre-processing:
  - Differences in Parcellation Scheme: number of ROIs / selection criteria / coverage
  - Differences in Metrics used to Capture FC Dynamics
  - Differences in classification/grouping algorithms: SVM / K-means / Similarity
  - Differences in validation schemes: None / Tasks / Populations
  
- ❖ **Comparison / Consolidation of Results is quite challenging.**
  
- ❖ **Some groups already working on potential clinical applications based on measures of dynamic FC**
  - Schizophrenia, Bipolar Disorder, Alzheimer's, Multiple Sclerosis...

**SOME  
METHODODOLOGICAL  
CONSIDERATIONS**

Perhaps the most commonly used strategy for examining dynamics.



What window type to use?

What window length?

What window step?

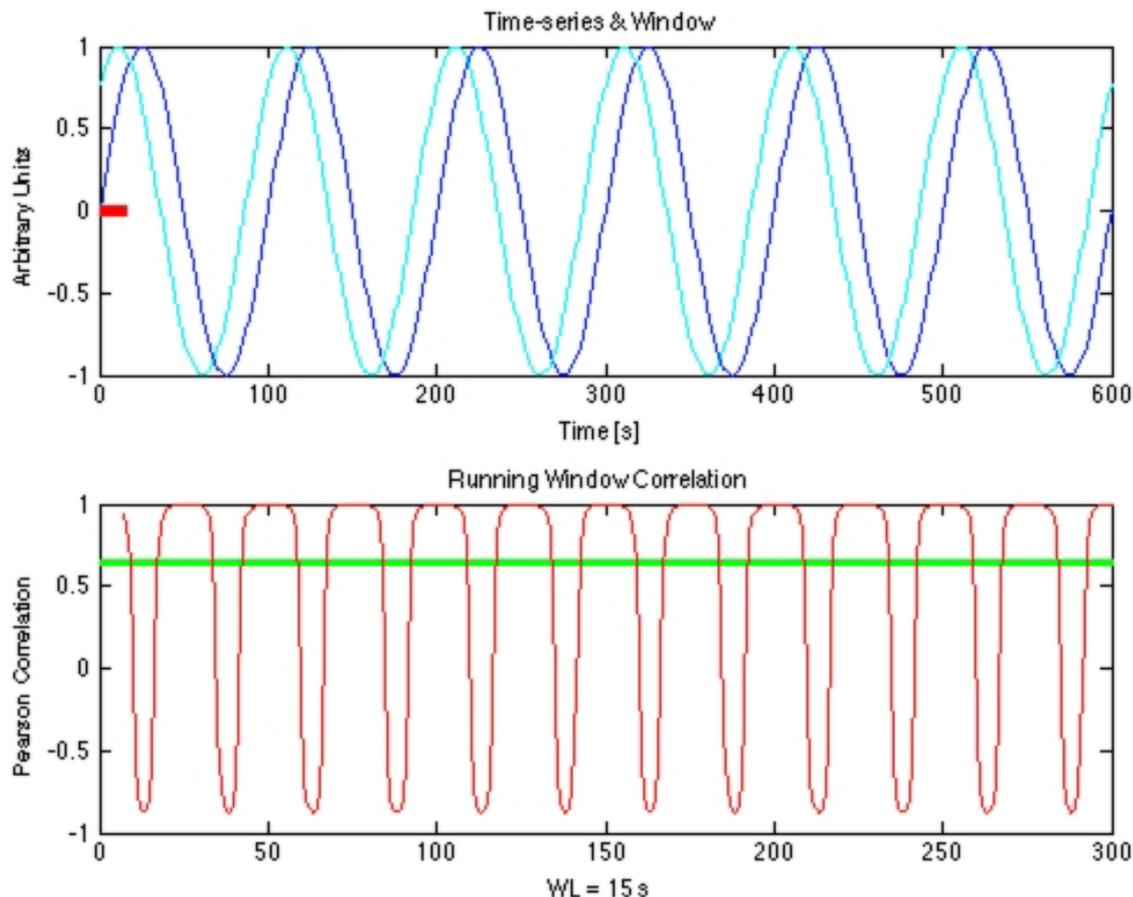
### PROS:

- It seems easy to interpret.
- It seems to capture phenomena with potential biological/neuronal relevance.

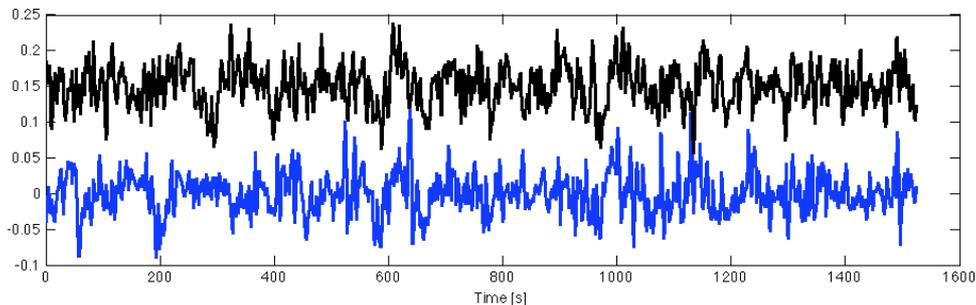
### CONS:

- Too small windows may render correlation estimates unreliable.
- Interpretation is more complex than it seems.

WL < 1 Period of slower fluctuation → Spurious fluctuations in correlation traces will appear

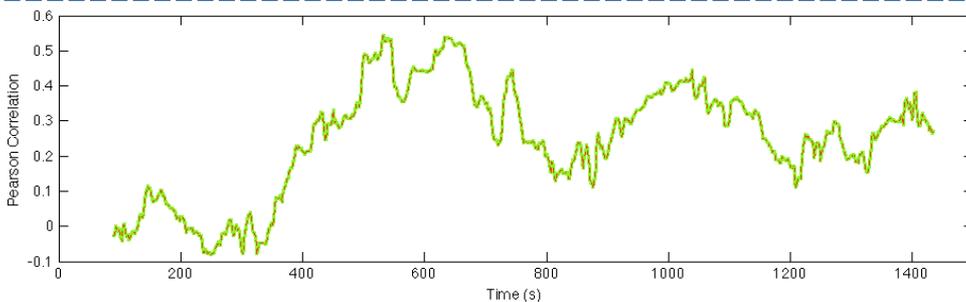


**WORK AROUND:** to avoid this confound, we must high pass filter the data ( $F_{\min}=1/WL$ ) according to the window lengths (WLs) used during the analysis



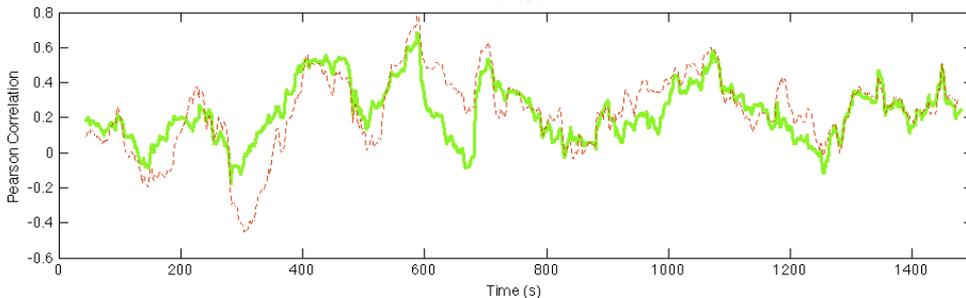
Time series of sliding window correlations  
between both ROIs

WL = 180s



— 0.006 – 0.18Hz

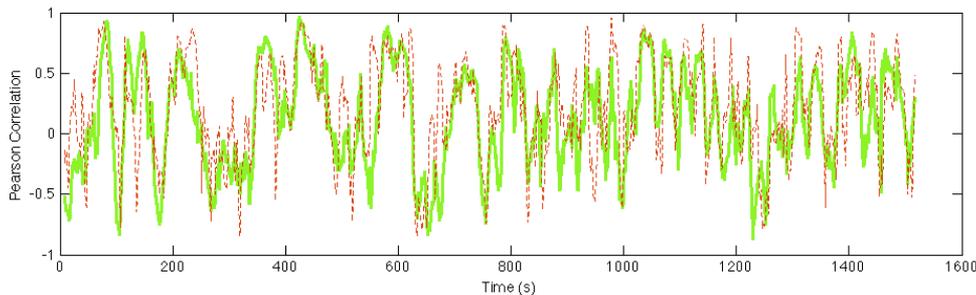
WL = 90s



— 0.011 – 0.18Hz

- - 0.006 – 0.18Hz

WL = 15s

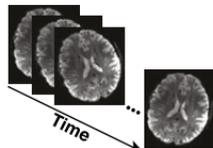


— 0.066 – 0.18Hz

- - 0.006 – 0.18Hz

1. Data Collection

7T, 2x2x2mm, TR=1.5"

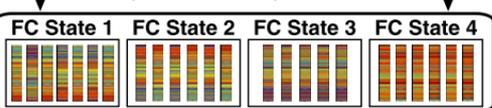


Task-Driven Cognitive States

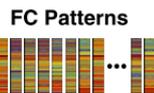


7. Validation

Visual, Quantitative, & Behavioral

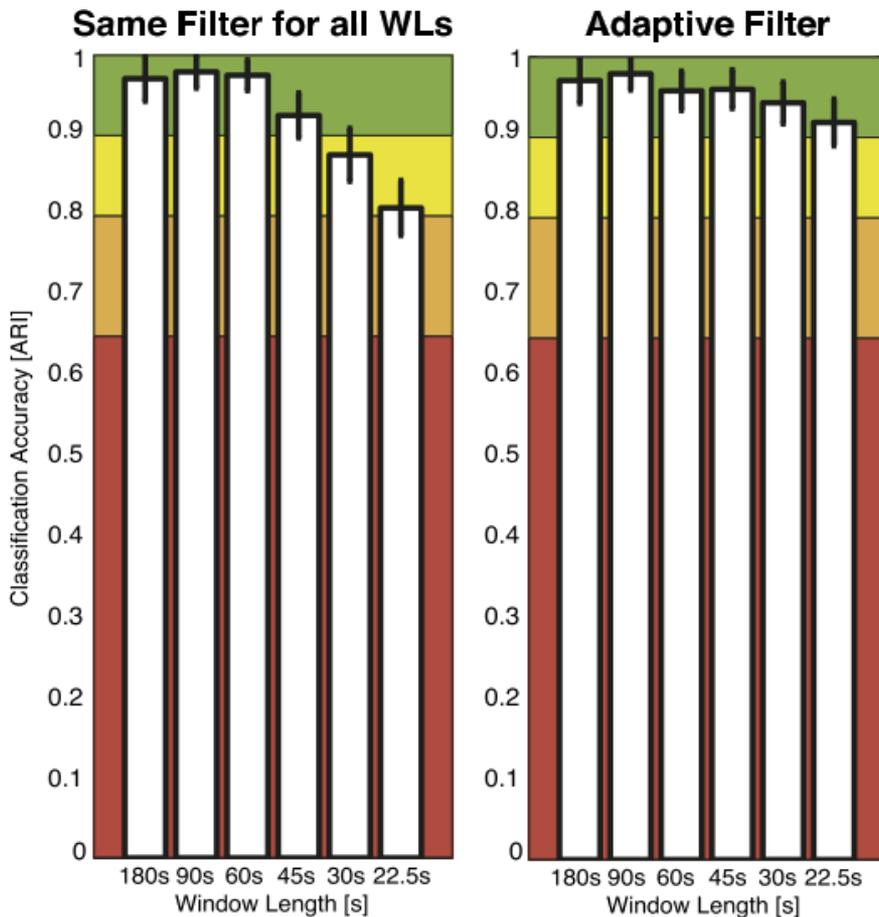


Data-Derived FC States

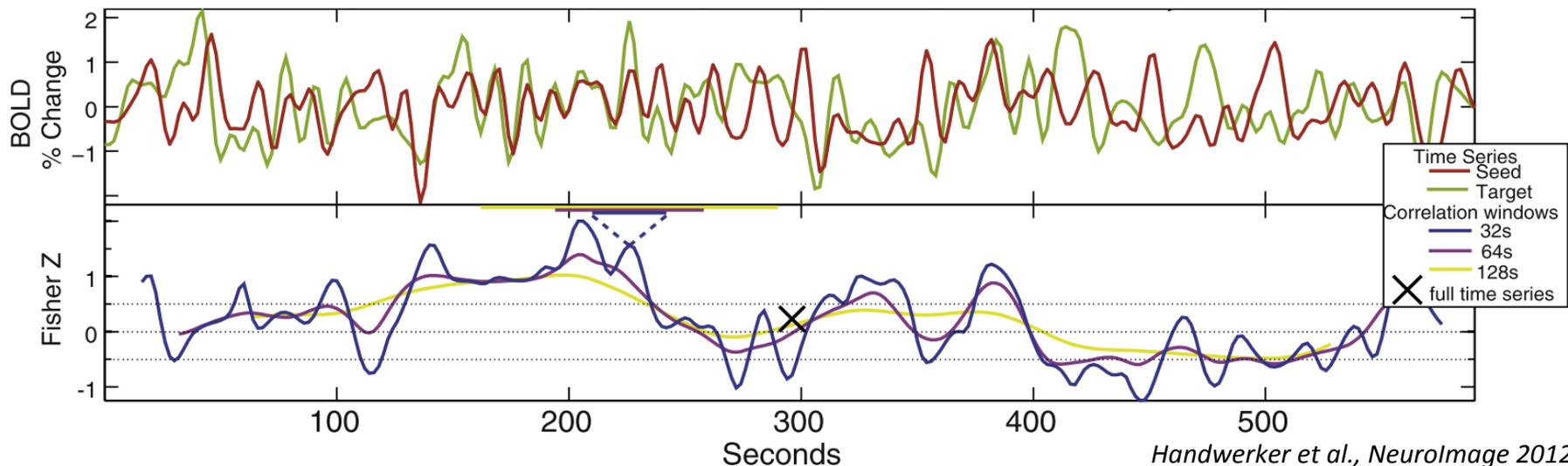


6. Clustering

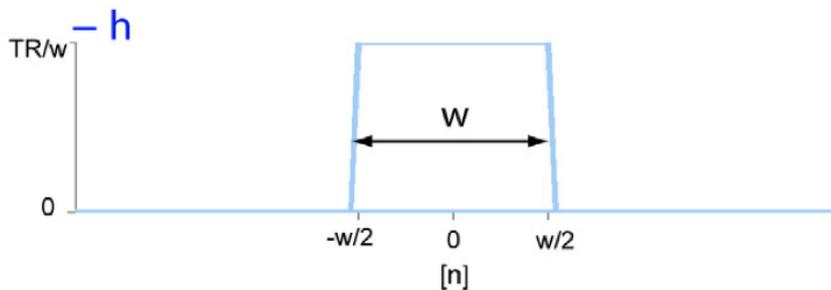
K-Means (k=4)



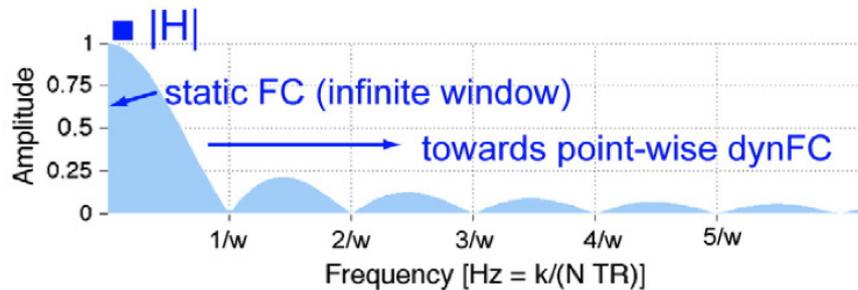
**COMMON OBSERVATION:** The longer the window, the less the observed variability in Dynamic FC.



**BE AWARE:** The sliding window acts as a low pass filter with cutoff frequency  $F_{max} = 1/WL$  on the resulting traces of dynamic connectivity (e.g., sliding window correlation traces).

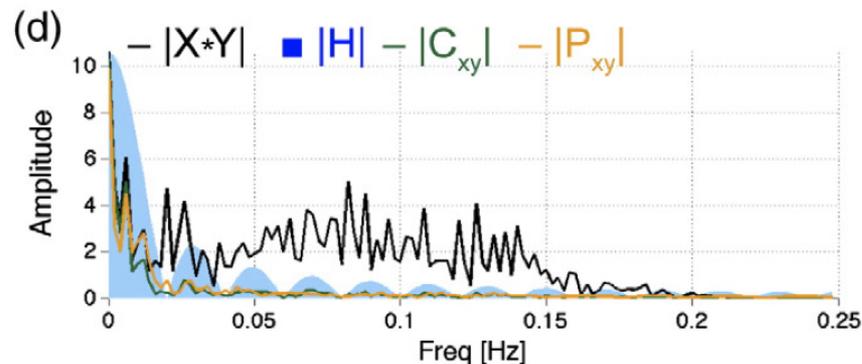
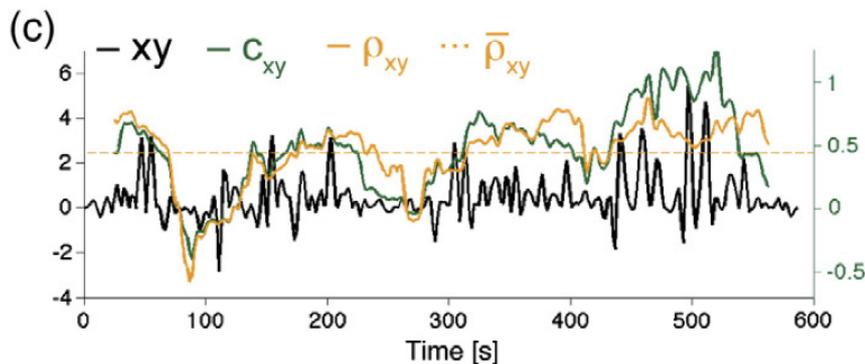
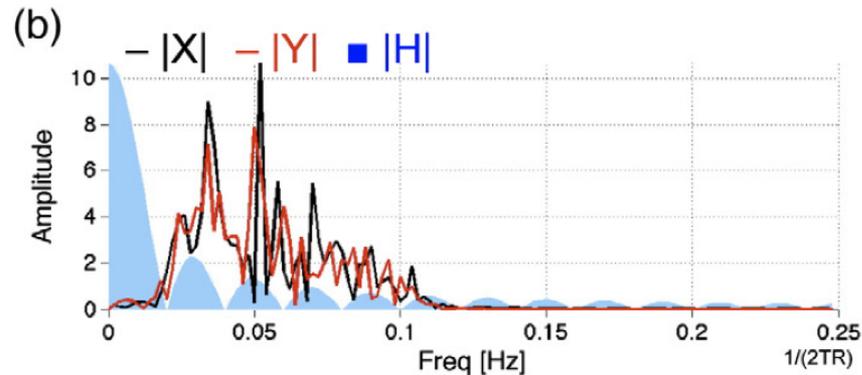
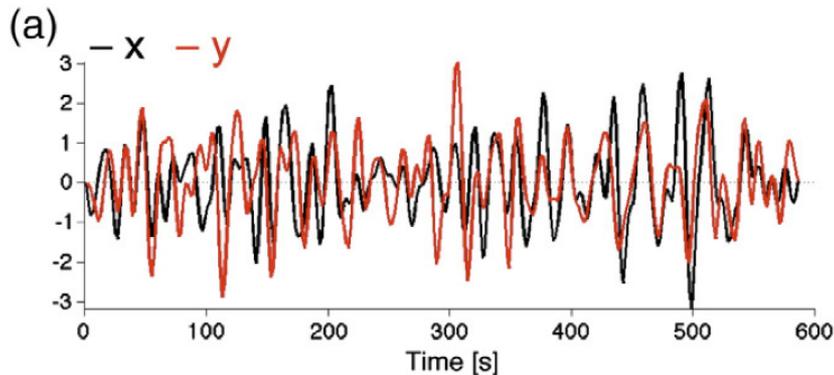


Window in Time Domain

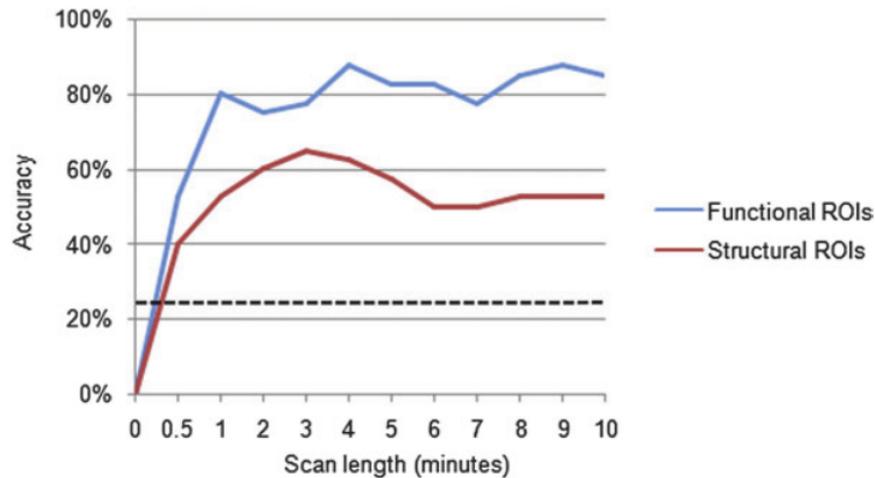


Window in Frequency Domain

$$WL = 50s \rightarrow F_{min\_signals} = F_{max\_observedDynamicConn} = 0.02 \text{ Hz}$$

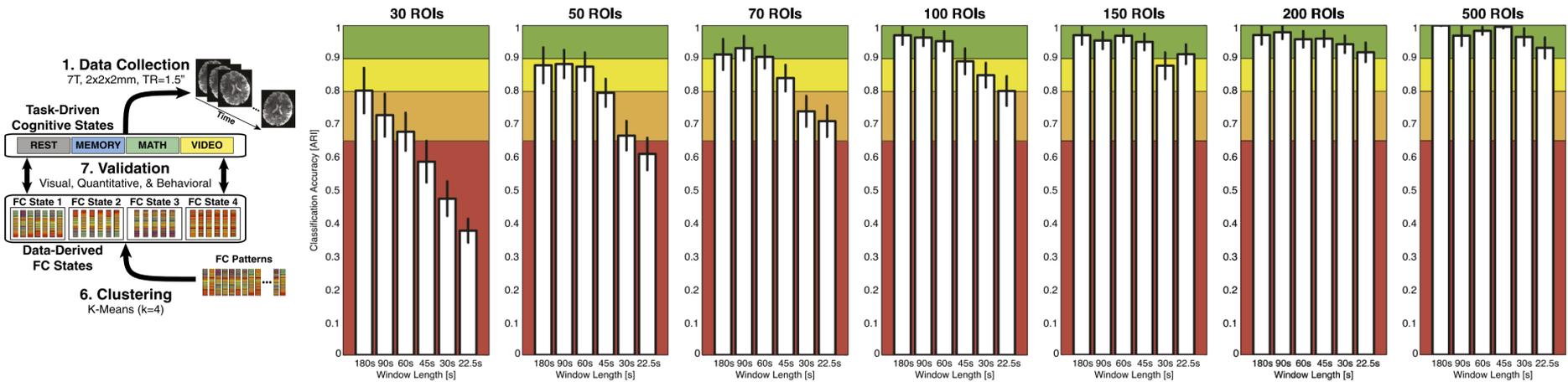


- (1) Spurious fluctuations in dynFC can be limited by appropriate high pass filtering ( $1/WL$ ).
- (2) Remaining fluctuations in dynFC will be low-pass filtered ( $1/WL$ ).
- (3) Smaller windows and/or longer TR  $\rightarrow$  greater influence of noise in estimation of dynFC.

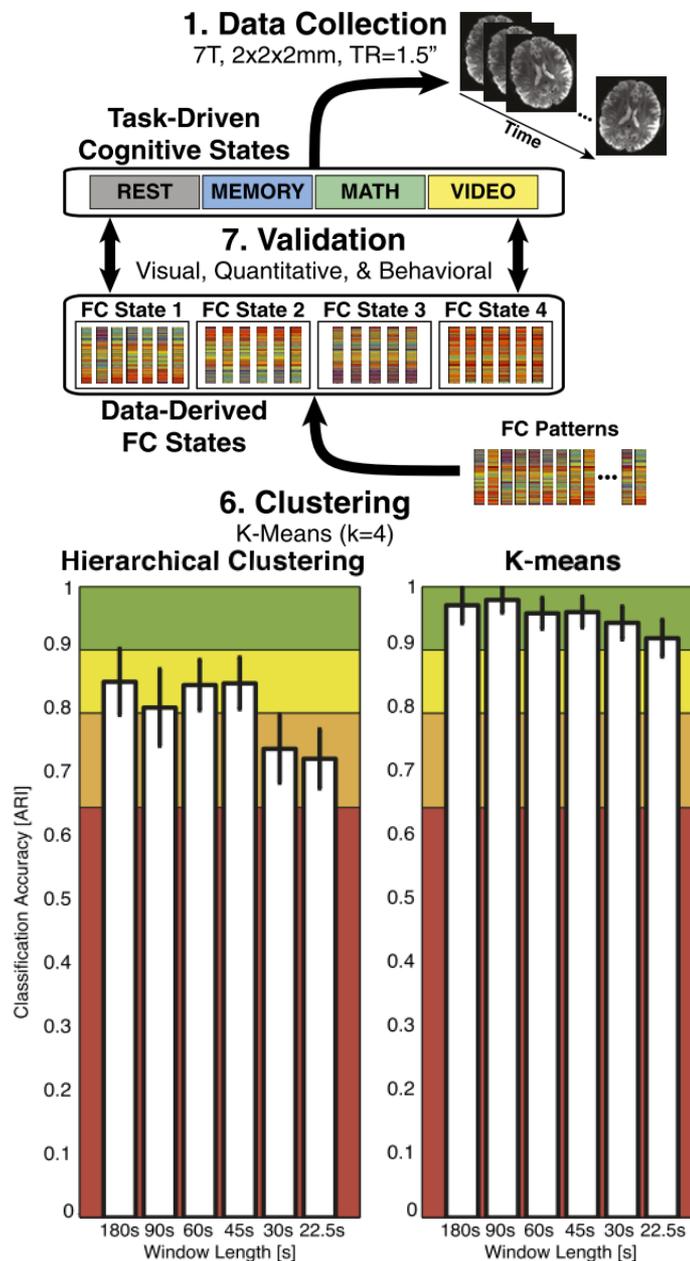


Functionally defined ROIs seem to perform better than Anatomically defined ROIs.

*Shirer et al. Cerebral Cortex 2012*



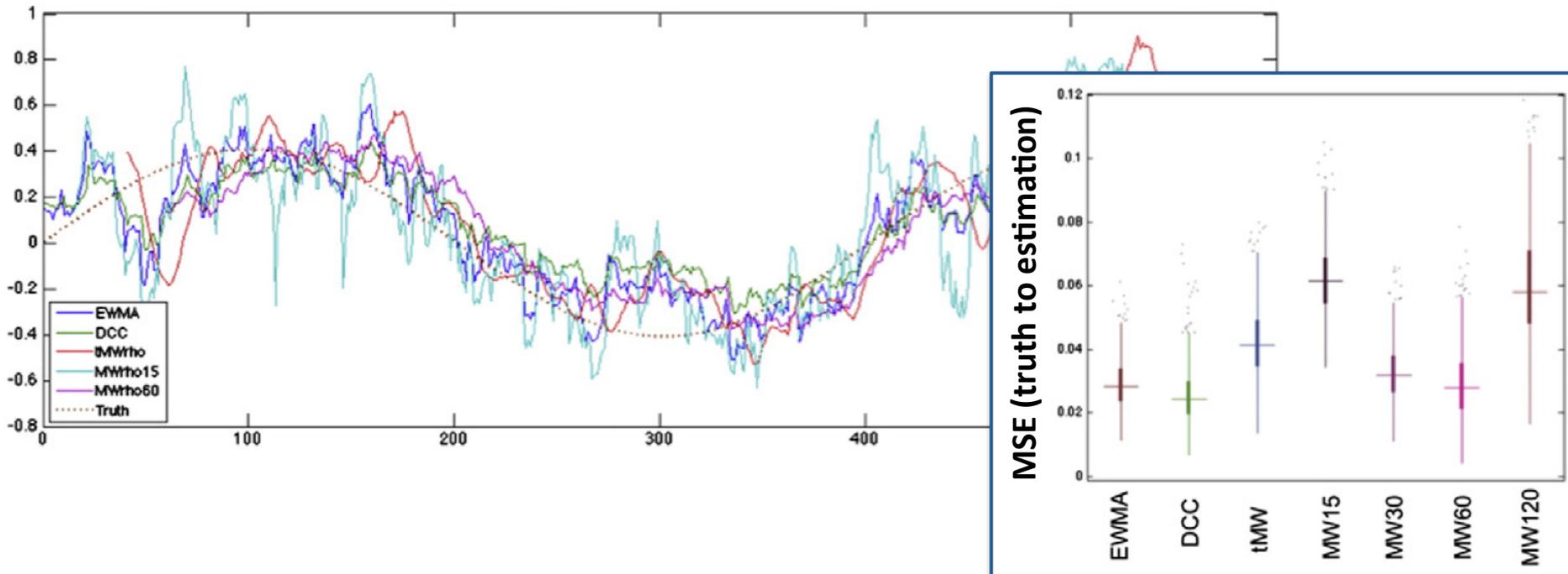
“More smaller ROIs” seem to perform better than “Less larger ROIS”



**DCC: A model for computation of time-varying variances and correlations in non-stationary time-series borrowed from the financial literature (multivariate volatility models).**

- Does not require a-priori selection of window length.
- Robust against previously discussed limitations of the sliding window correlation.

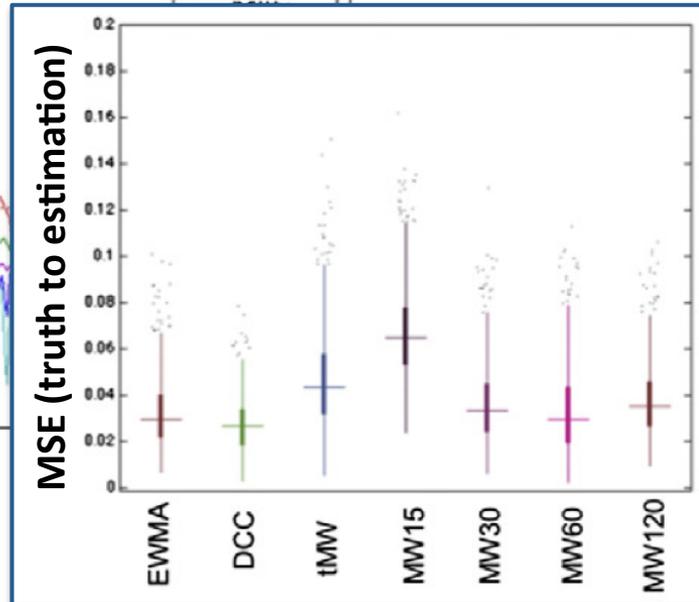
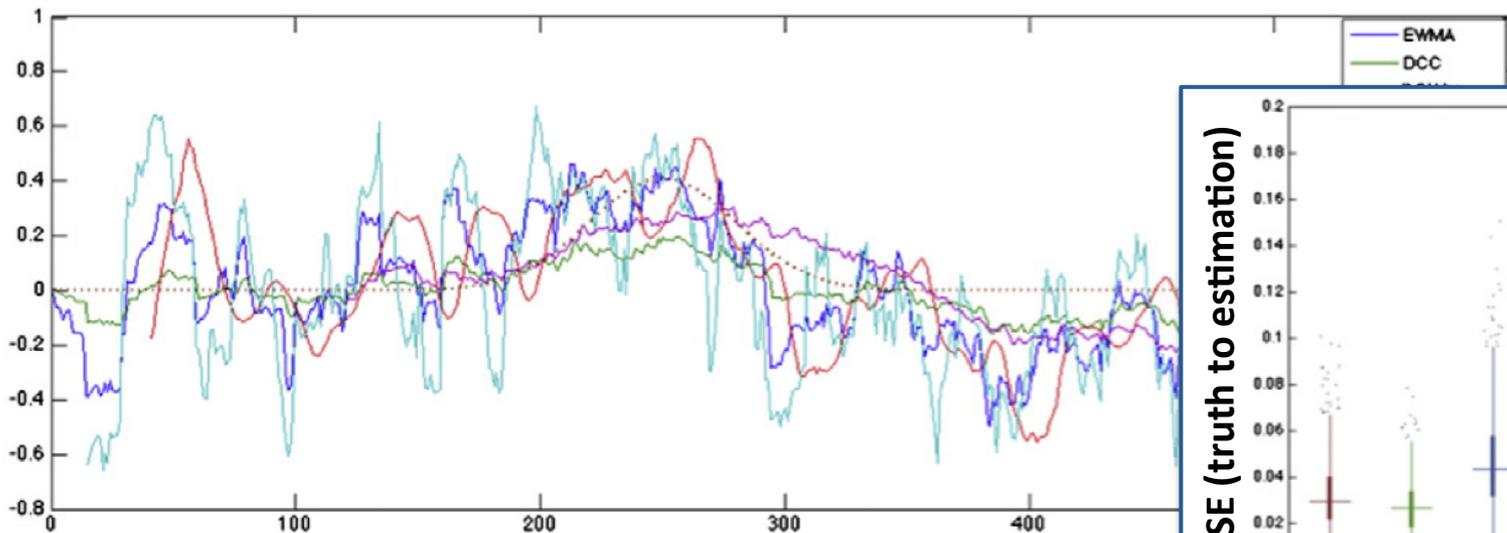
Slowly-varying Periodic change in correlation



**DCC: A model for computation of time-varying variances and correlations in non-stationary time-series borrowed from the financial literature (multivariate volatility models).**

- Does not requires a-priori selection of window length.
- Robust against previously discussed limitations of the sliding window correlation.

### Transient State Changes

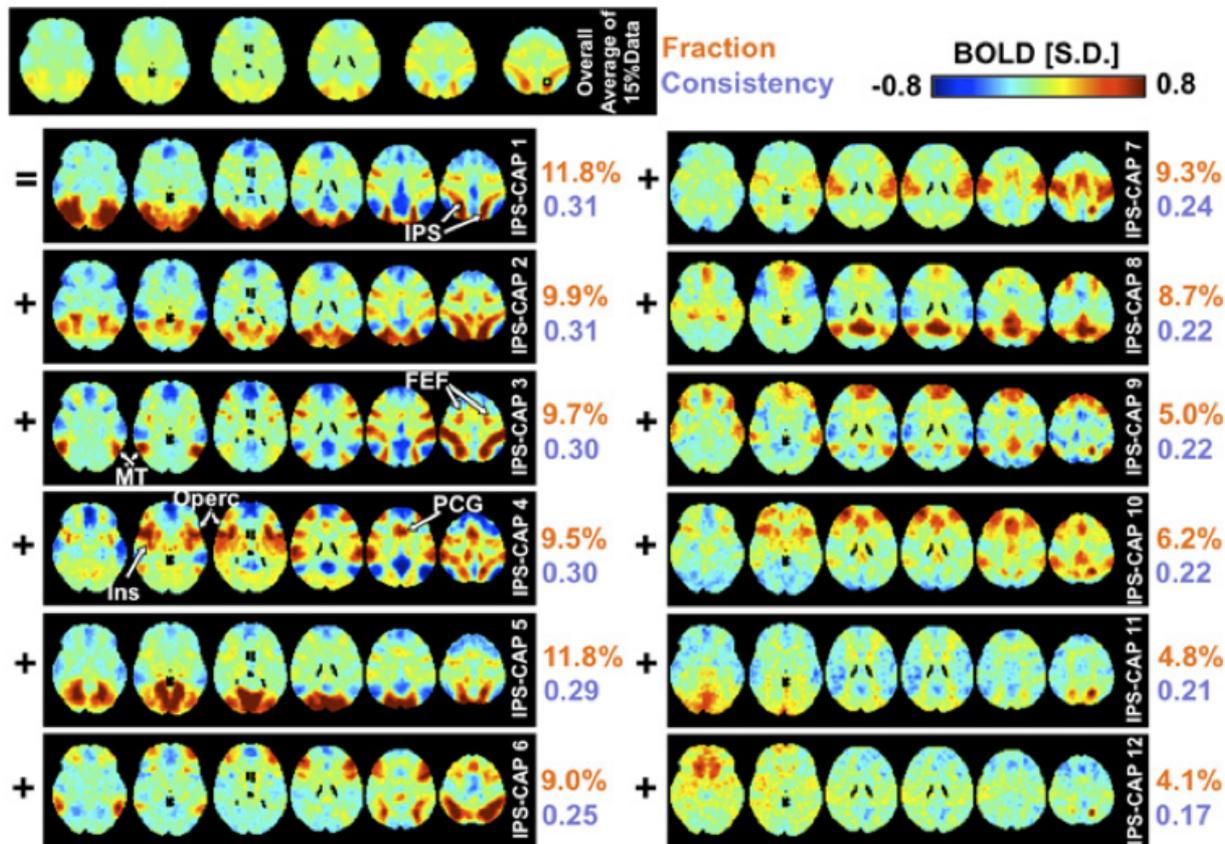


- Its ability to capture neuronal/cognitive meaningful fluctuations ought to be tested.
- Computation time increases linearly with number of ROIs.

### ❖ Co-Activation Patterns (CAPs)

Cluster selected individual BOLD volumes of a resting-state scan based on spatial similarity.

Use resulting cluster centroids, defined as “co-activation patterns” (CAPs), to characterize a set of representative instantaneous configurations of BOLD activity.



Example: Decomposition of the Dorsal Attention Network in 12 CAPs

Lui et Dyun, PNAS, 2013

- ❖ BOLD Functional Connectivity exhibit rich spatio-temporal dynamic behavior at the scale of seconds to minutes.
- ❖ Short-term patterns significantly differ from whole-scan average patterns. Some of these short-term patterns re-occur in time and are consistent across subjects.
- ❖ Emerging evidence suggests that dynamic FC metrics may index changes in macroscopic neural activity patterns underlying critical aspects of cognition and behavior.
- ❖ Temporal features of FC could serve as a disease biomarker.

- 
- ❖ Better understand which methods actually capture biologically and neuronally relevant functional connectivity dynamics.
  - ❖ It is unclear the extent to which dynamic FC is best conceptualized as a multi-stable state space wherein multiple discrete patterns recur, or whether it simply varies along a continuous state space.
  - ❖ The study of dynamic FC raises the issue that the concept of a “network” is rather elusive, hinging (among other factors) upon the time-scale over which it is defined.

### ❖ Data Acquisition

- Spatial <-> Temporal Resolution → Temporal Resolution is key.
- Consider the use of Multi-Band/Multi-Slice Acquisition Techniques.

### ❖ Data Pre-processing

- Use appropriate filtering.
- Consider using a combination of methods.
- Temporal Windows of interest ( 25s – 60s).

### ❖ Parcellation Scheme

- Functionally defined ROIs seem to outperform anatomically defined ROIs.
- “More smaller ROIs” better than “Less larger ROIs”.

### ❖ Interpretational Challenges

- Control for obvious sources of variability: motion/physiological noise/scanner.
- When possible, design your experiment so that you can validate results.

### ❖ Two Excellent Reviews

- Hutchison et al. “Dynamic Functional Connectivity: Promise, Issues, and Interpretations” *NeuroImage* 80:360-378 (2012).
- Calhoun et al. “The Chronnectome: Time-varying connectivity networks as the next frontier in fMRI Data Discovery” *Neuron* 84(2): 262 – 274 (2014).

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