Dynamic Resting State fMRI

Javier González-Castillo

Section on Functional Imaging Methods, NIMH, NIH

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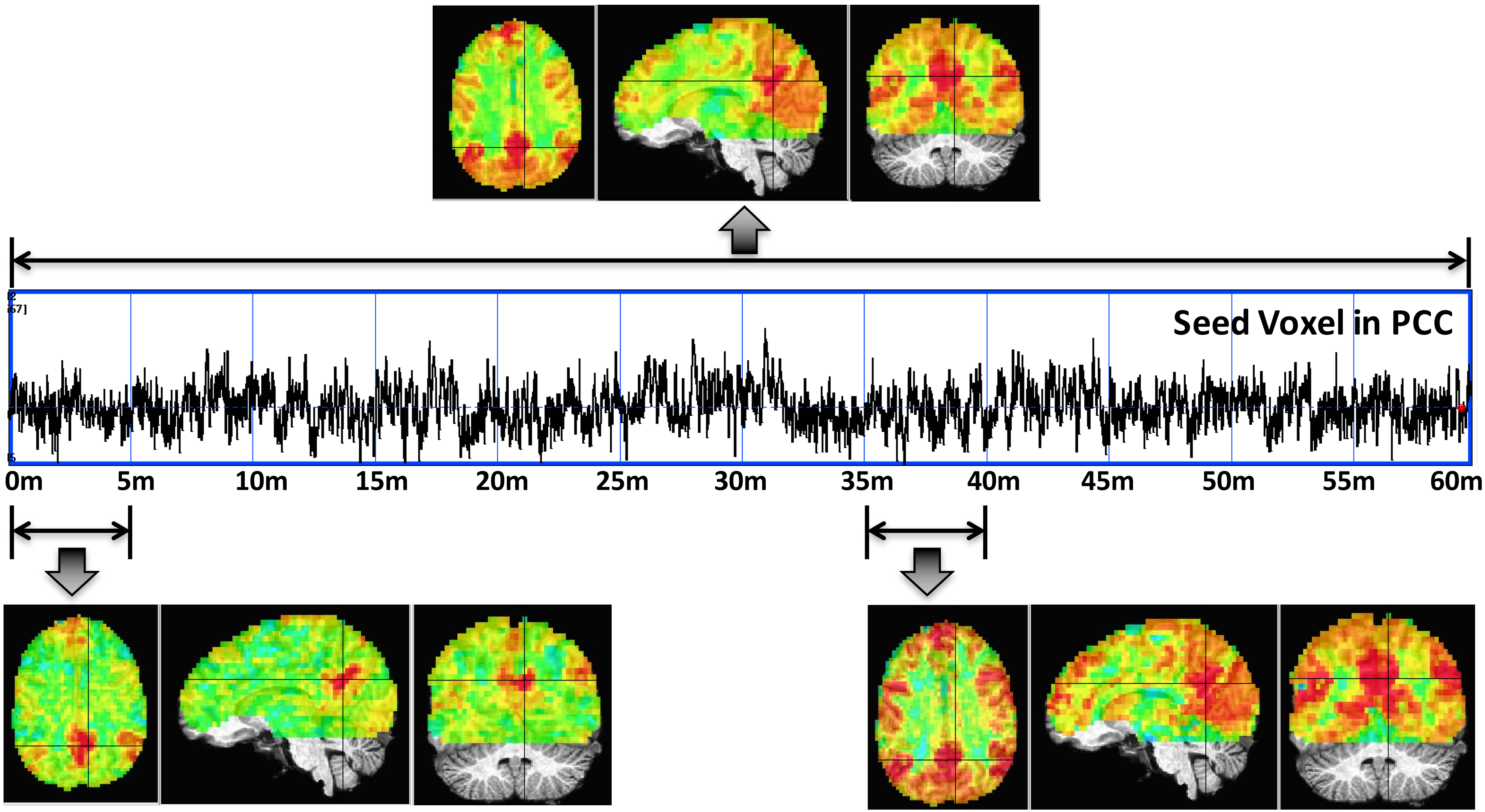
Agenda

- **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**

WHAT IS BOLD FUNCTIONAL CONNECTIVITY DYNAMICS

fMRI Connectivity Dynamics: DEFINITION

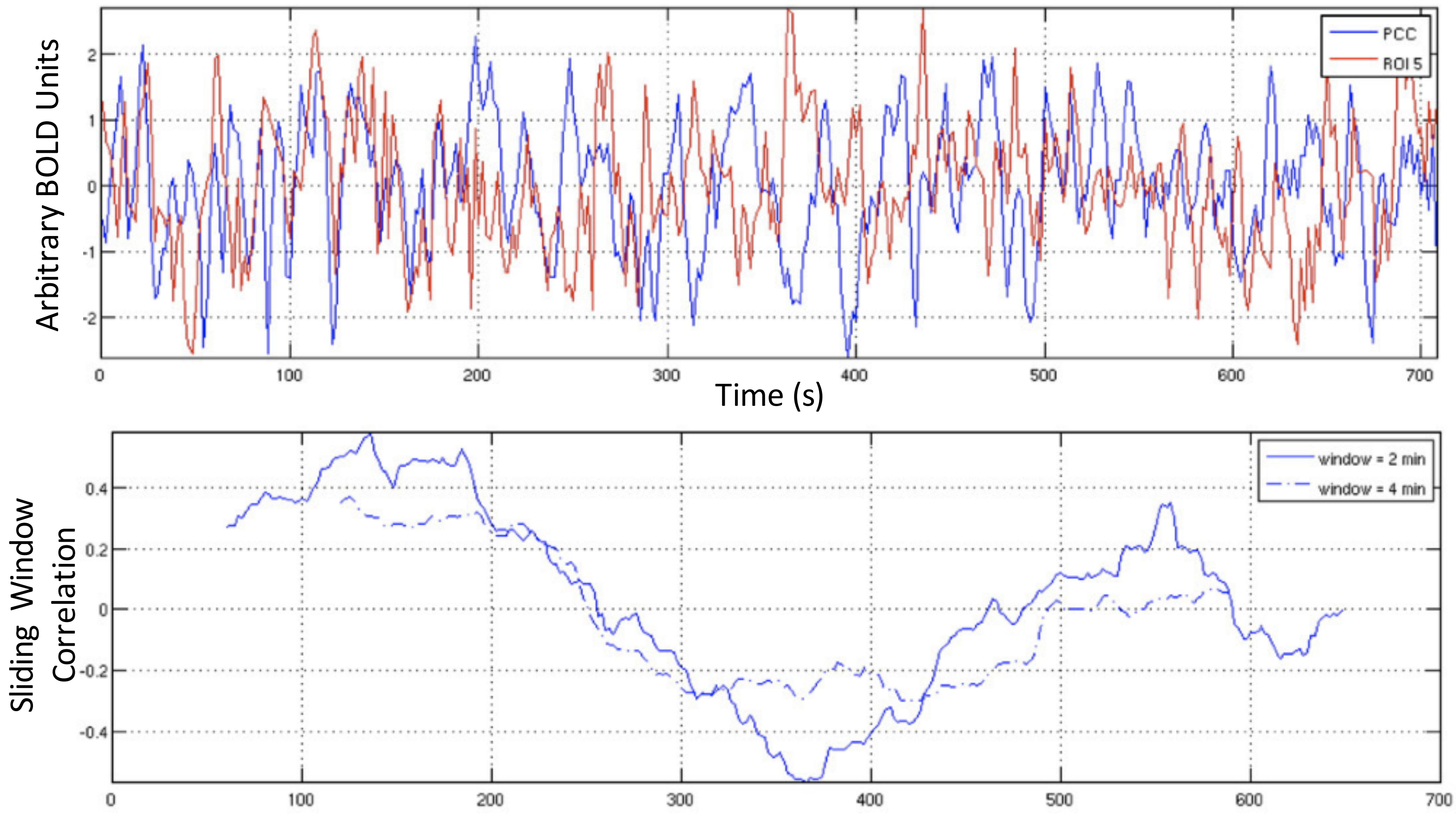


60 Minutes of Continuous Rest Data | TR = 1s

Gonzalez-Castillo et al., Frontiers in Neuroscience 2014

Original Observations (I)

"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…."



Chang & Glover, NeuroImage 2009

Original Observations (I):Dynamic behavior varies across regions

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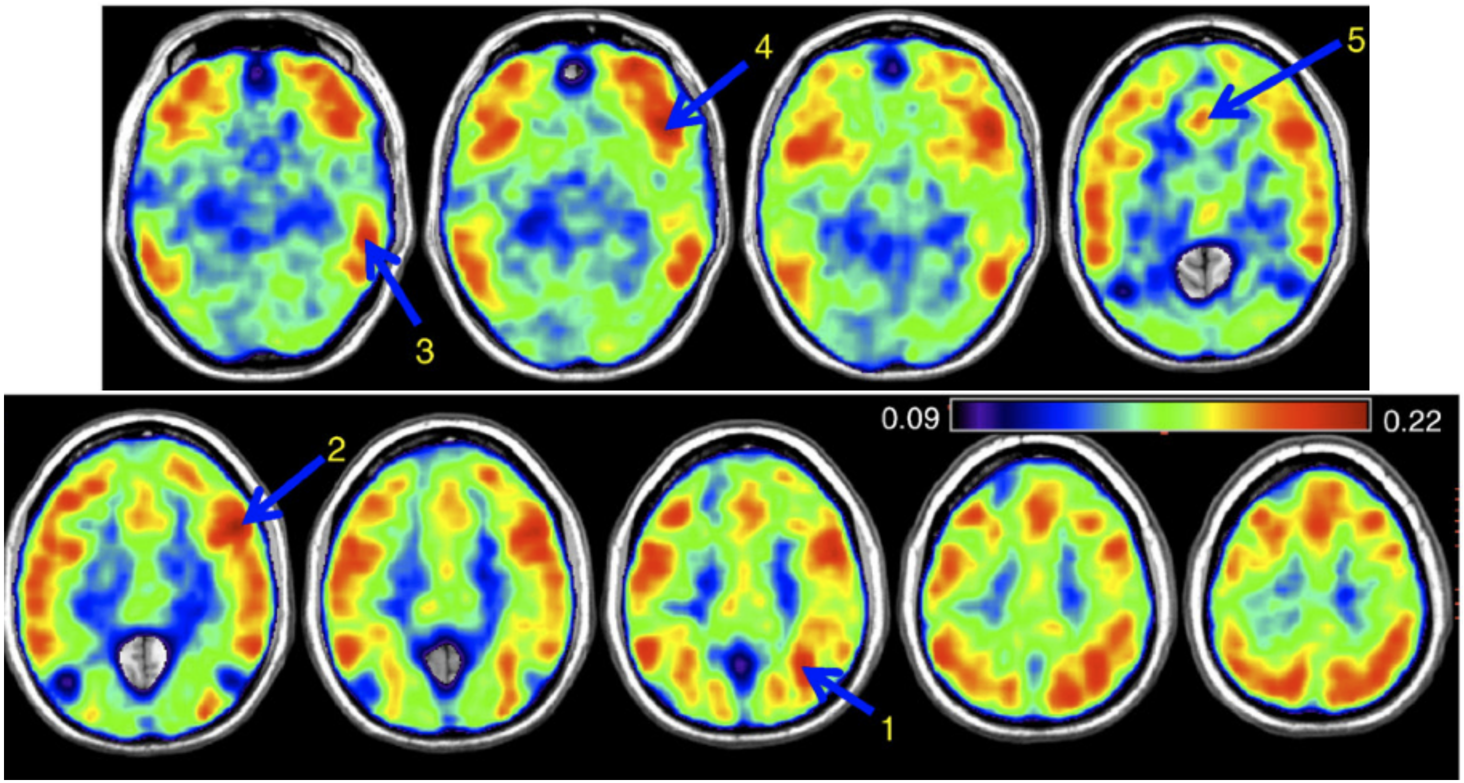
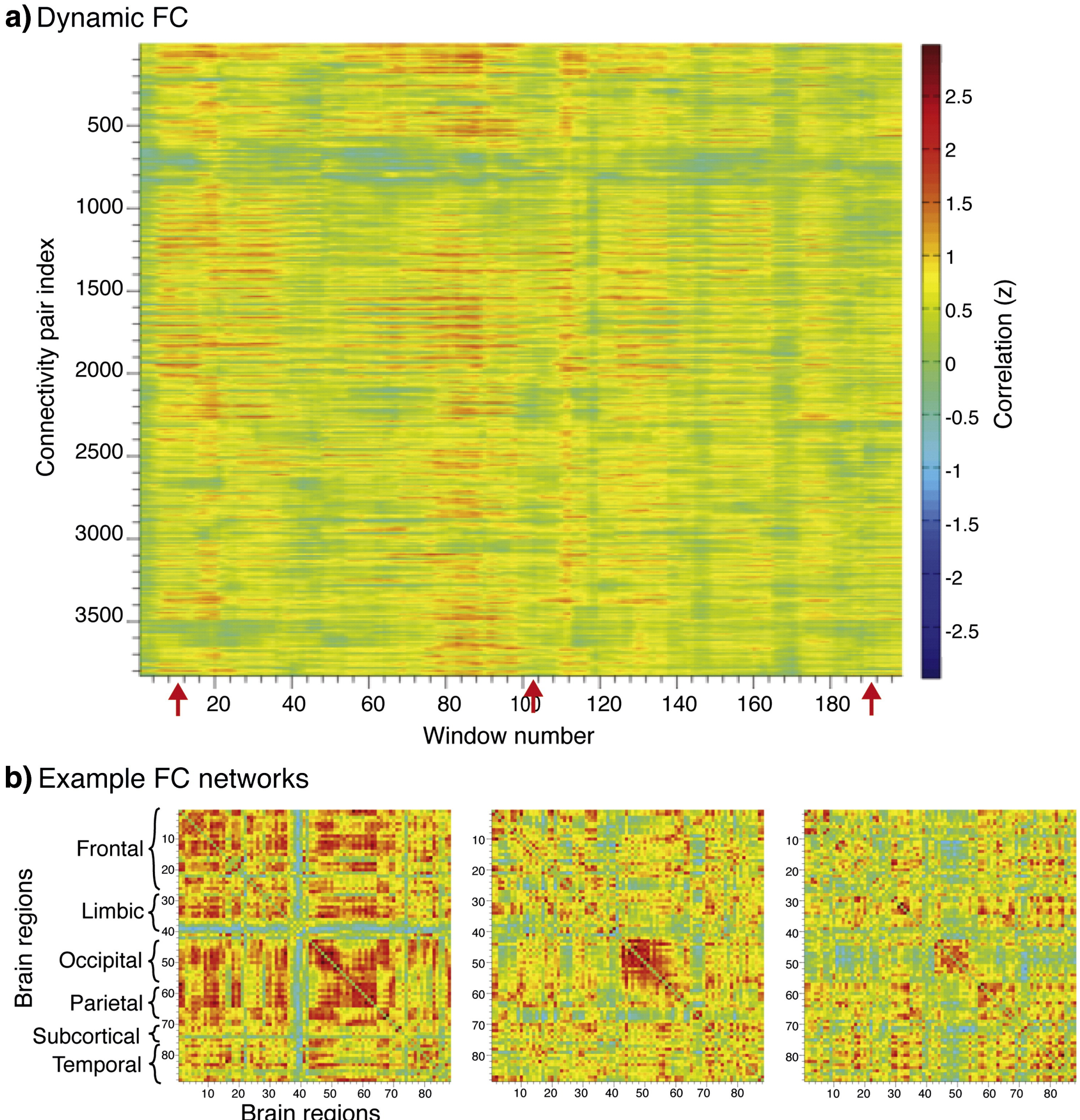


"…Although it is unclear whether the observed coherence and phase variability can be attributed to residual noise or modulation of cognitive state, the present results illustrate that resting-state functional connectivity is not static, and it may prove valuable to consider measures of variability, in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

Chang & Glover, NeuroImage 2009

Original Observations (II): Short Term FC can strongly deviate from Average Patterns

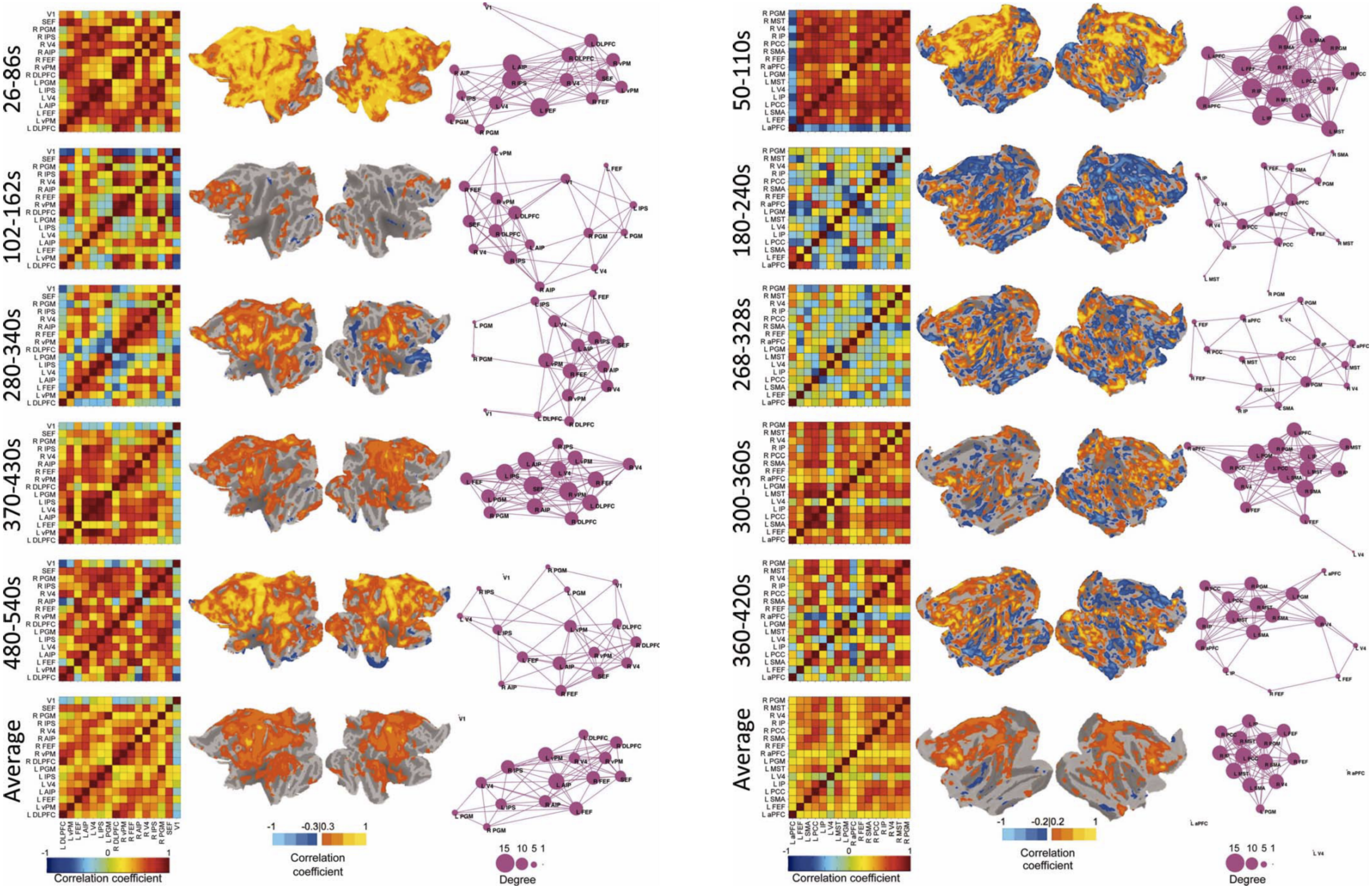


Leonardi et al. NeuroImage 2013

Original Observations (III): Dynamic FC also present in anaesthetized monkeys

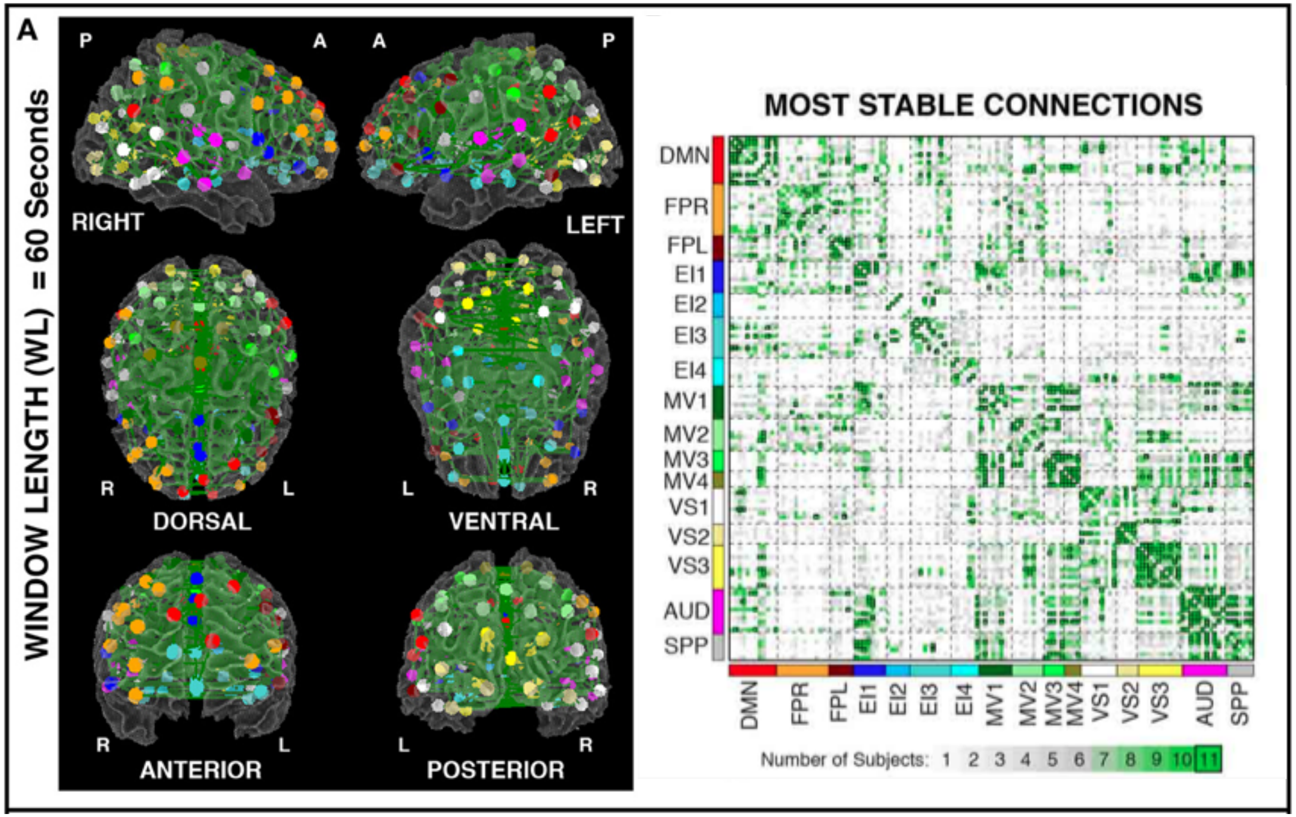
AWAKE HUMANS

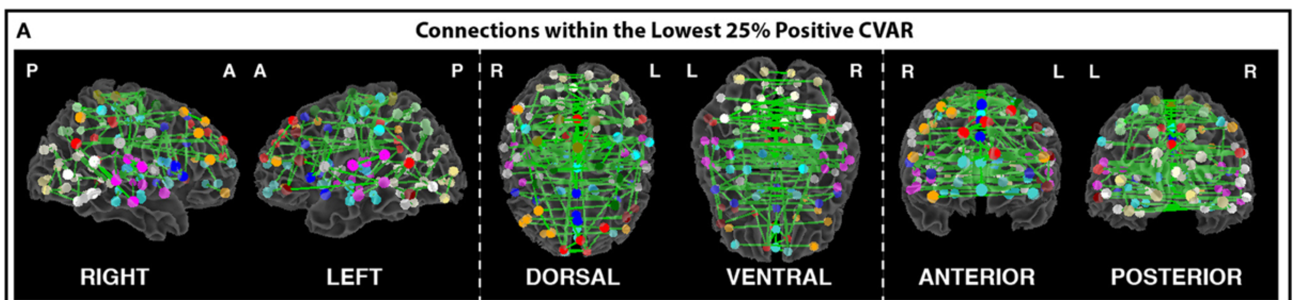
ISOFLURANE-ANESTHESIZED MONKEY



Hutchison et al., Hum Brain Mapping 2013

Spatial Distribution of Short Term FC Stability (I) – Most Stable Connections





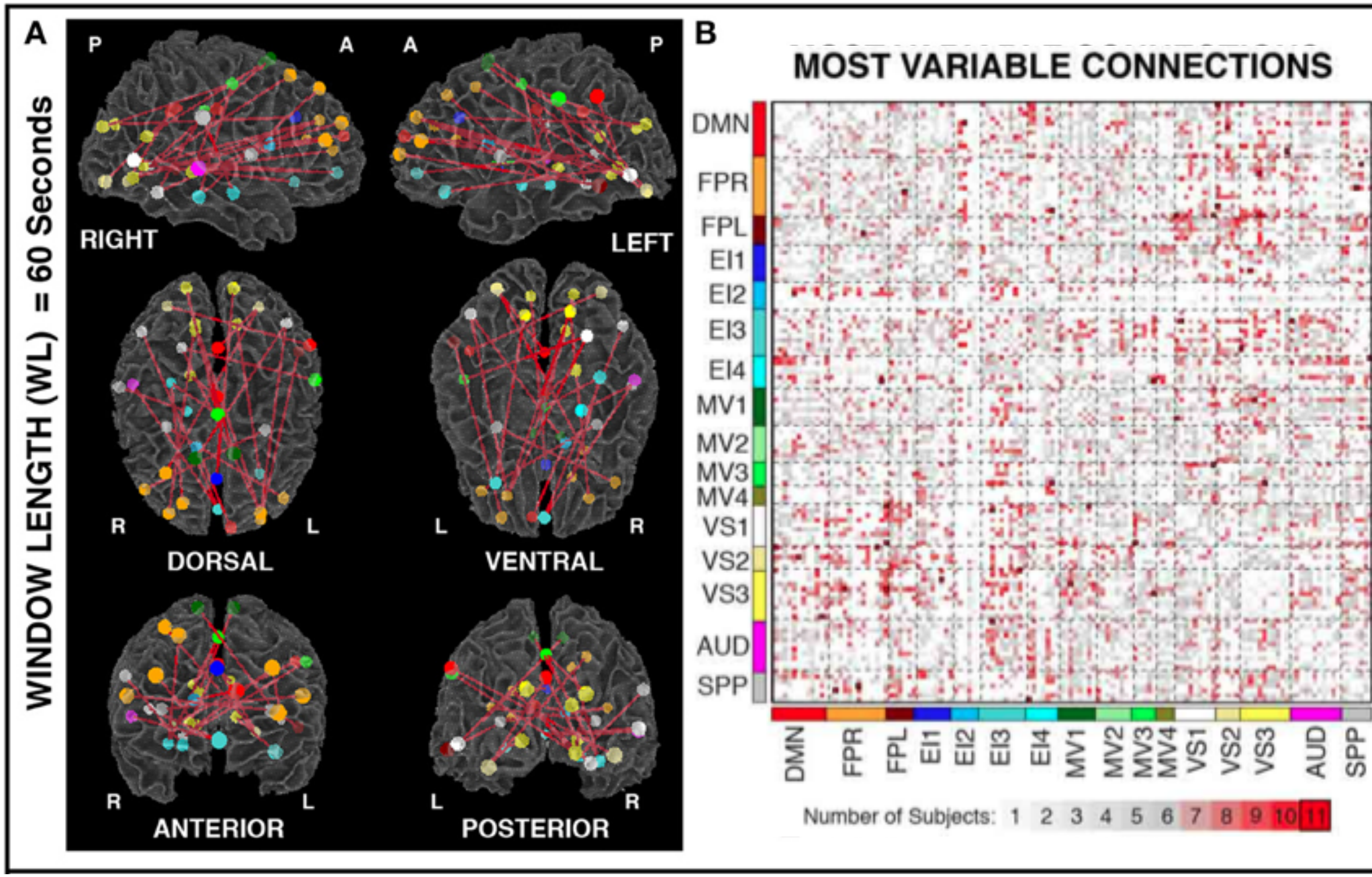
Mostly symmetric, inter-hemispheric connections between homologous right/left regions.

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.

Gonzalez-Castillo et al., Frontiers in Neuroscience 2014

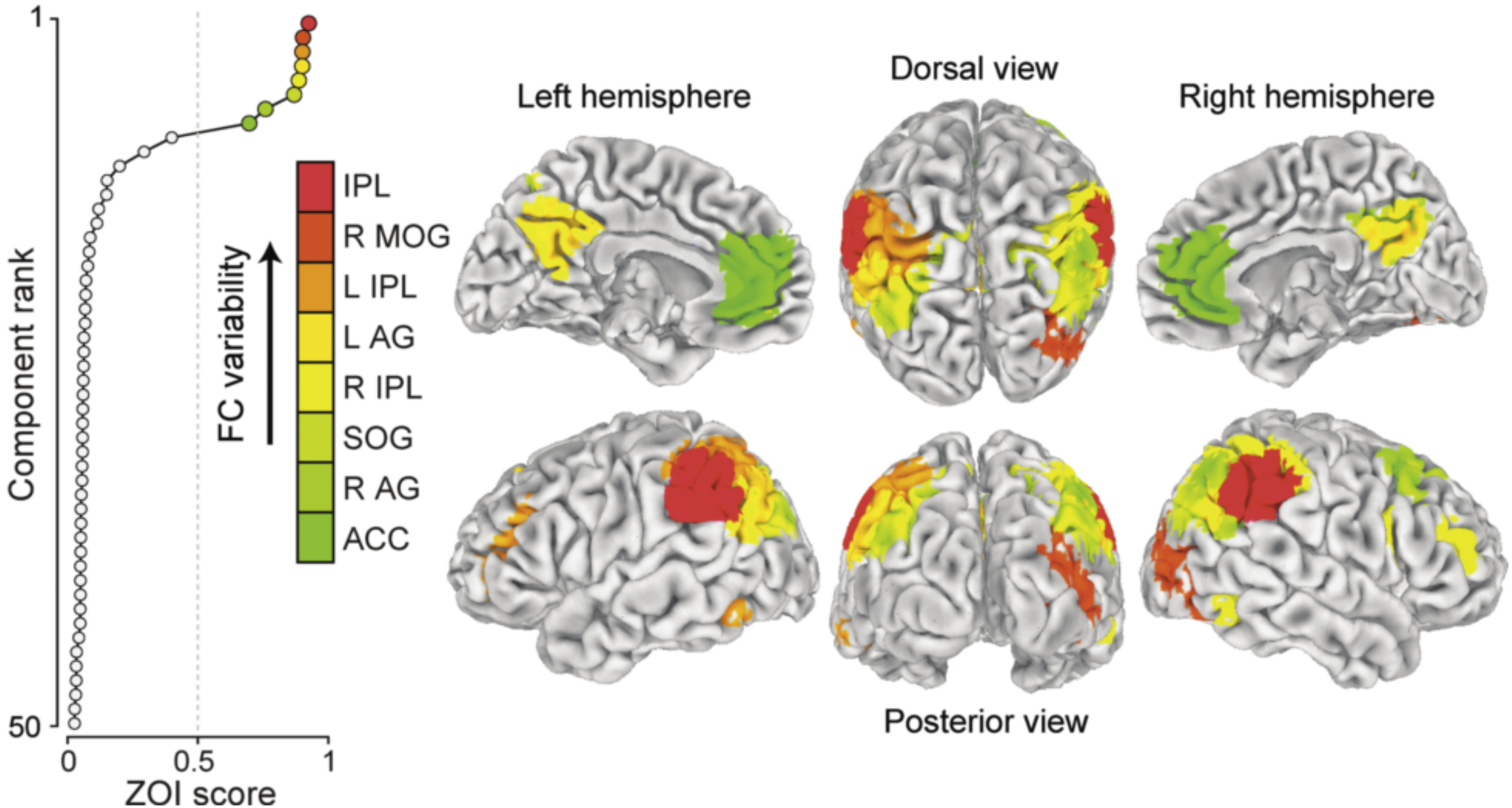
Spatial Distribution of Short Term FC Stability (I) – Most Variable Connections



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

Gonzalez-Castillo et al., Frontiers in Neuroscience 2014

Spatial Distribution of Short Term FC Stability (II)

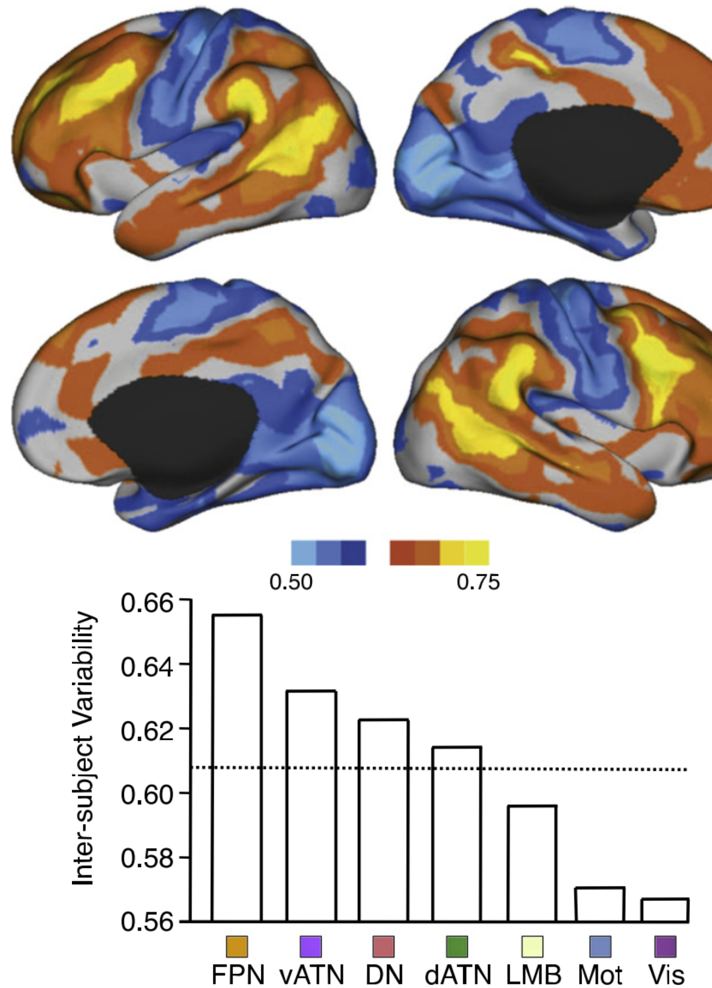


<u>**ZONE OF INSTABILITY**</u>: Set of Intrinsic Connectivity Networks with the most variable FC based on approx. 6 min long rest scans acquired on a group of 405 young adults and using a window length of 44 seconds.

Allen et al. Cerebral Cortex 2014

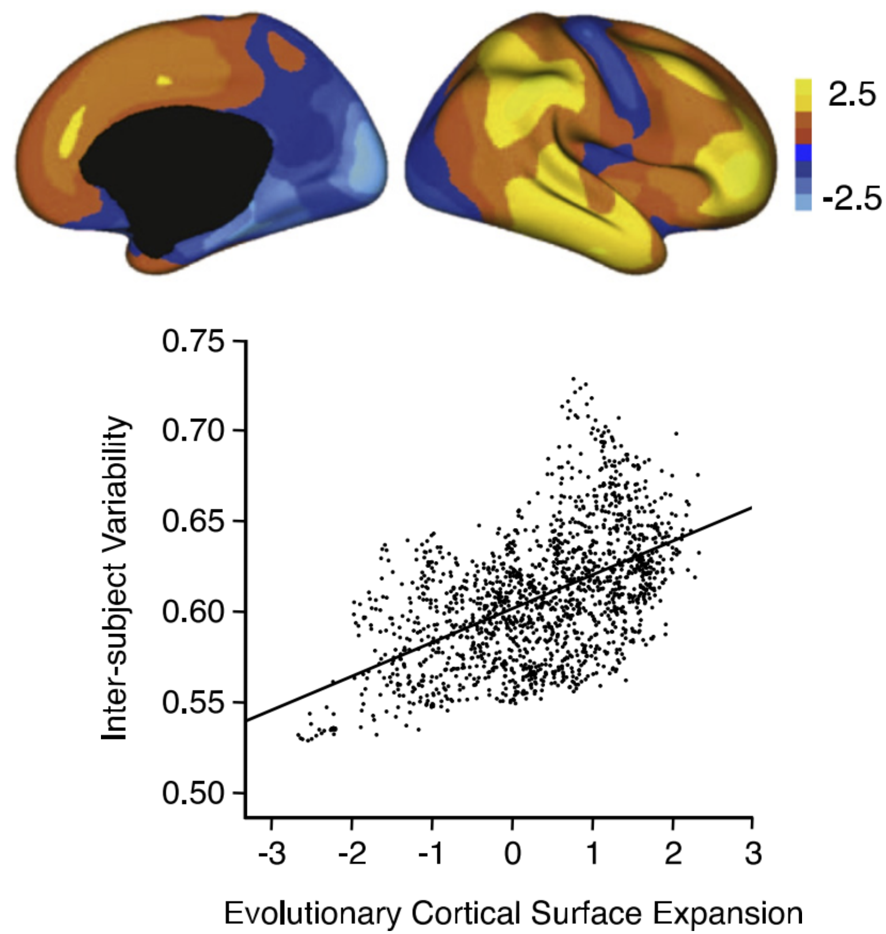
Overlap with regions of high inter-subject variability in stationary FC

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

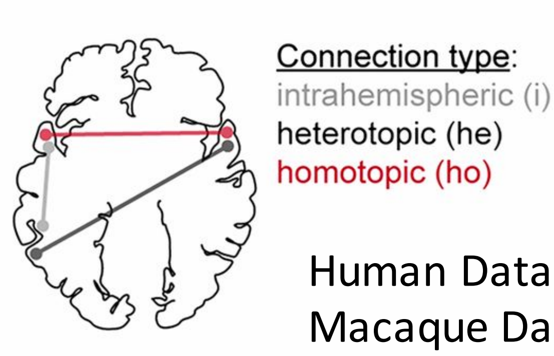


Functional Connectivity variability is highly correlated with evolutionary cortical surface expansion.

23 Subjects | 5 scans over 6 months | 6 min long rest scans

Mueller et al. Neuron, 2013

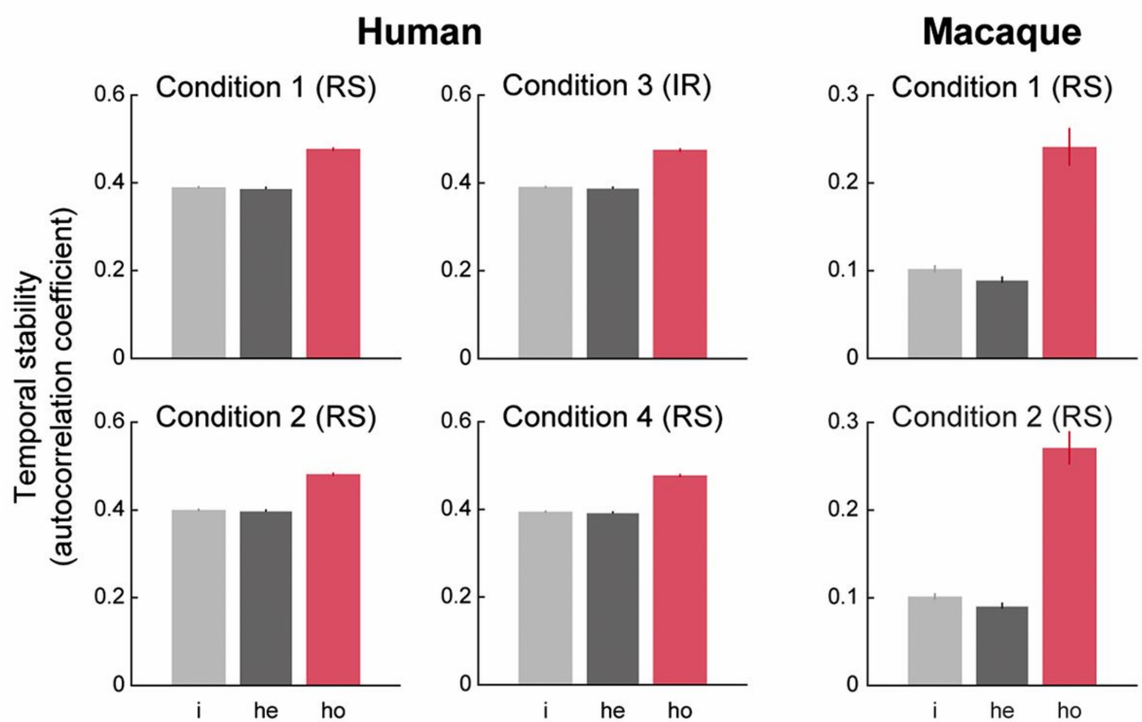
FC Dynamics & Anatomical Connectivity (II)



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

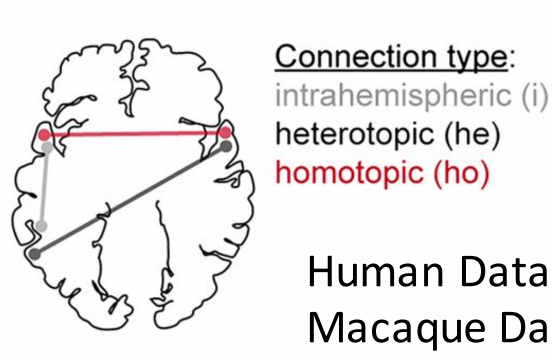
Across conditions & species, Homotopic FC is the most stable of all 3 types of connections.



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

Shen et al. PNAS 2015

FC Dynamics & Anatomical Connectivity (II)



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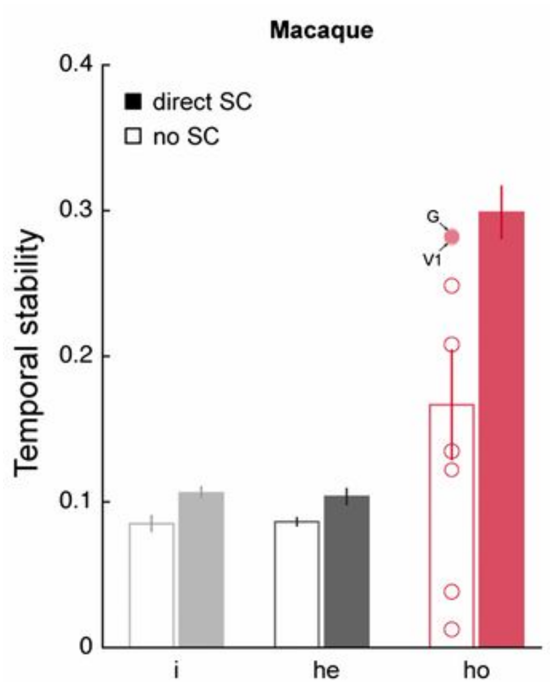
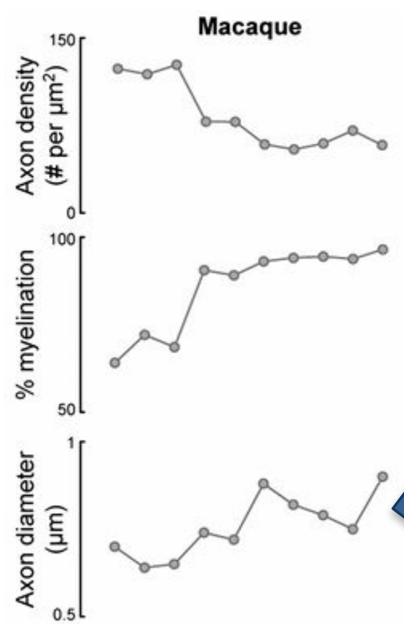
Macaque Data: 1 Condition Light Anesthesia

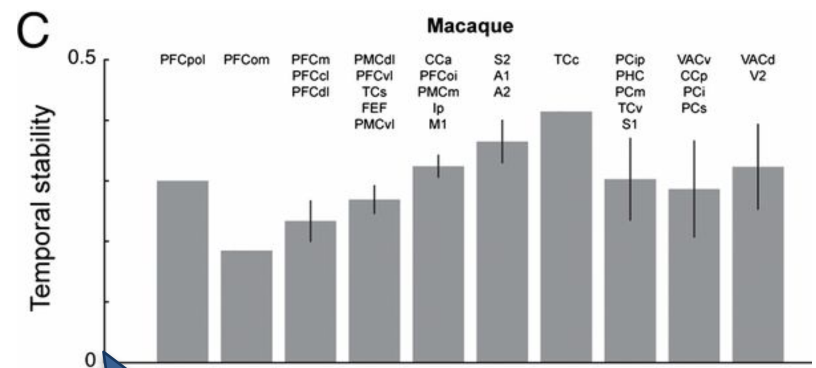
Temporal stability of homotopic FC is facilitated by direct anatomical projections and their conduction characteristics





Anterior ←→ Posterior

Profile of temporal stability for homotopic connections with direct structural connectivity

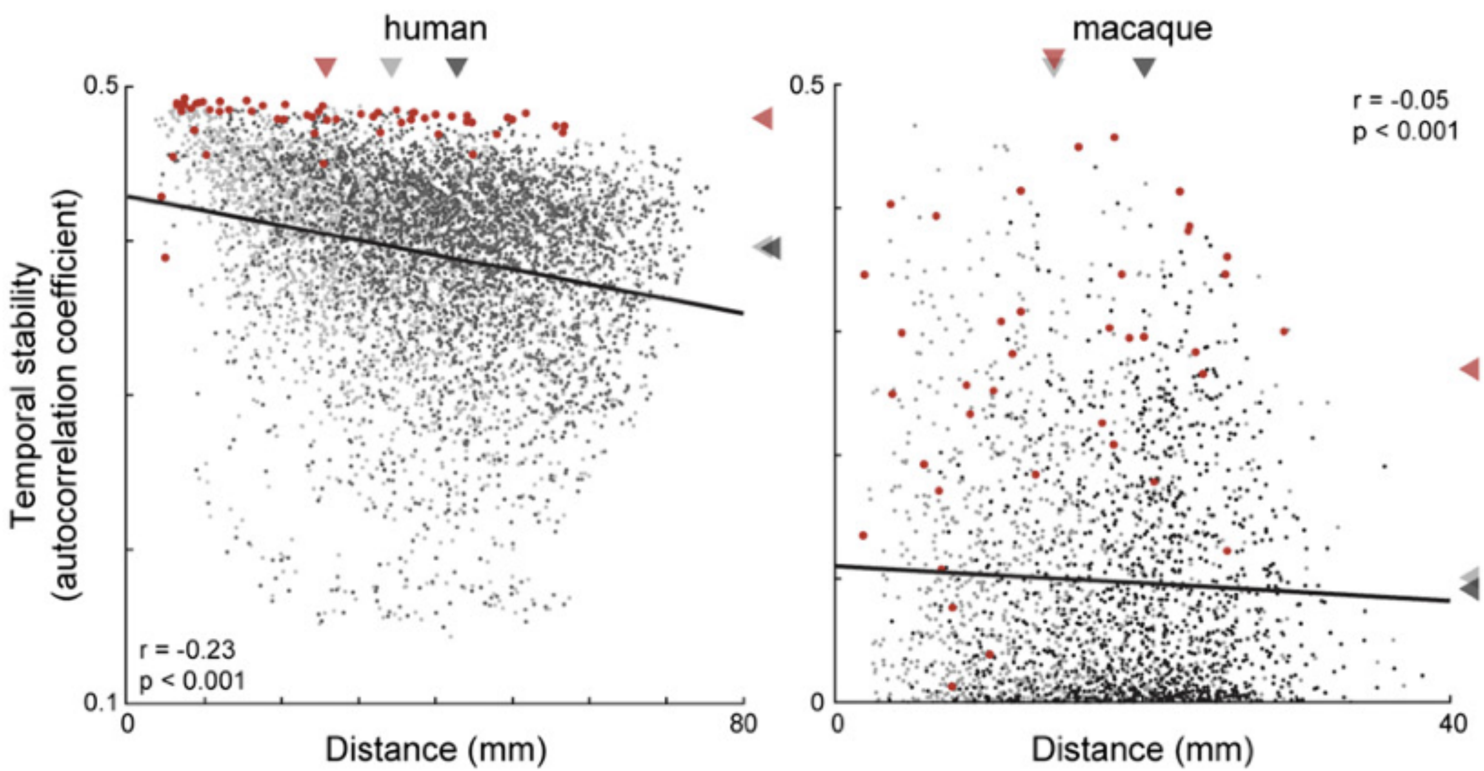


Anterior ←→ Posterior

Shen et al. PNAS 2015

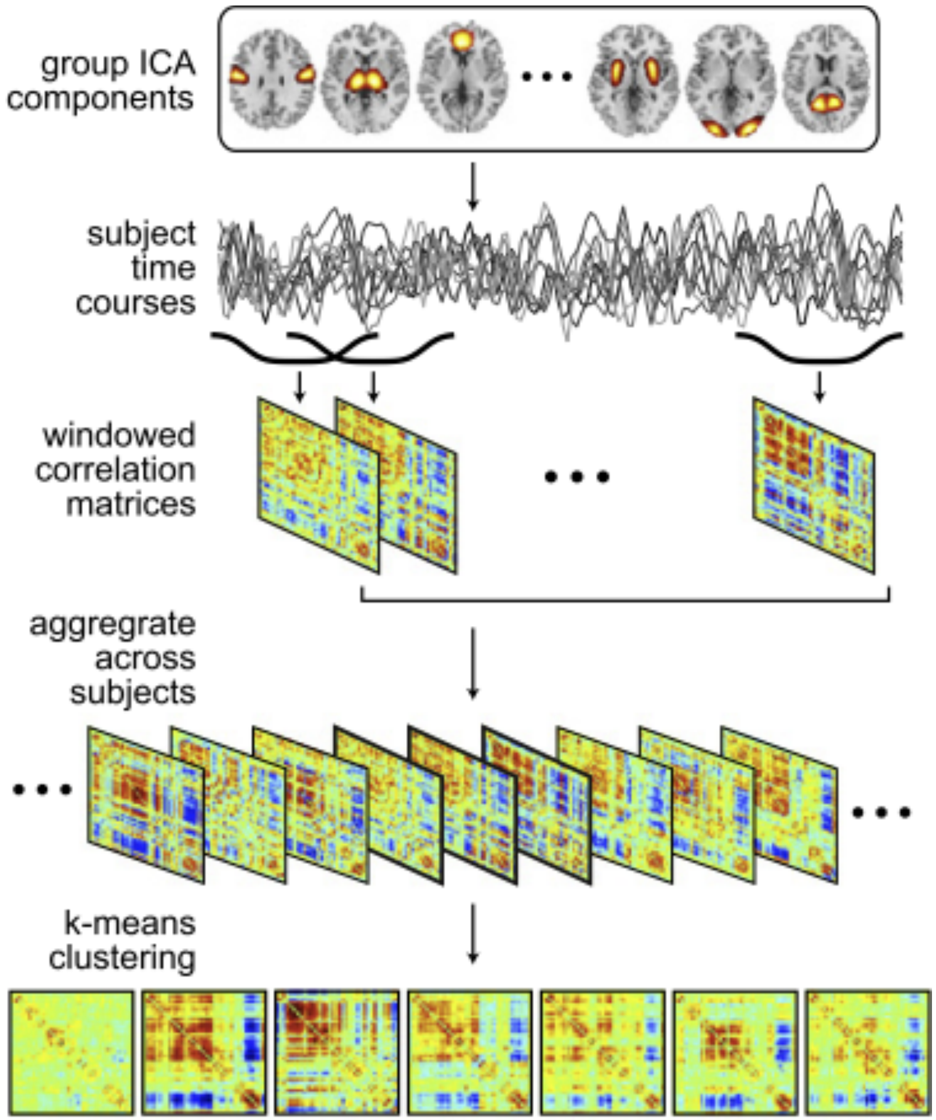
FC Dynamics cannot be explained simply by distance

(5) FC Stability independent of distance



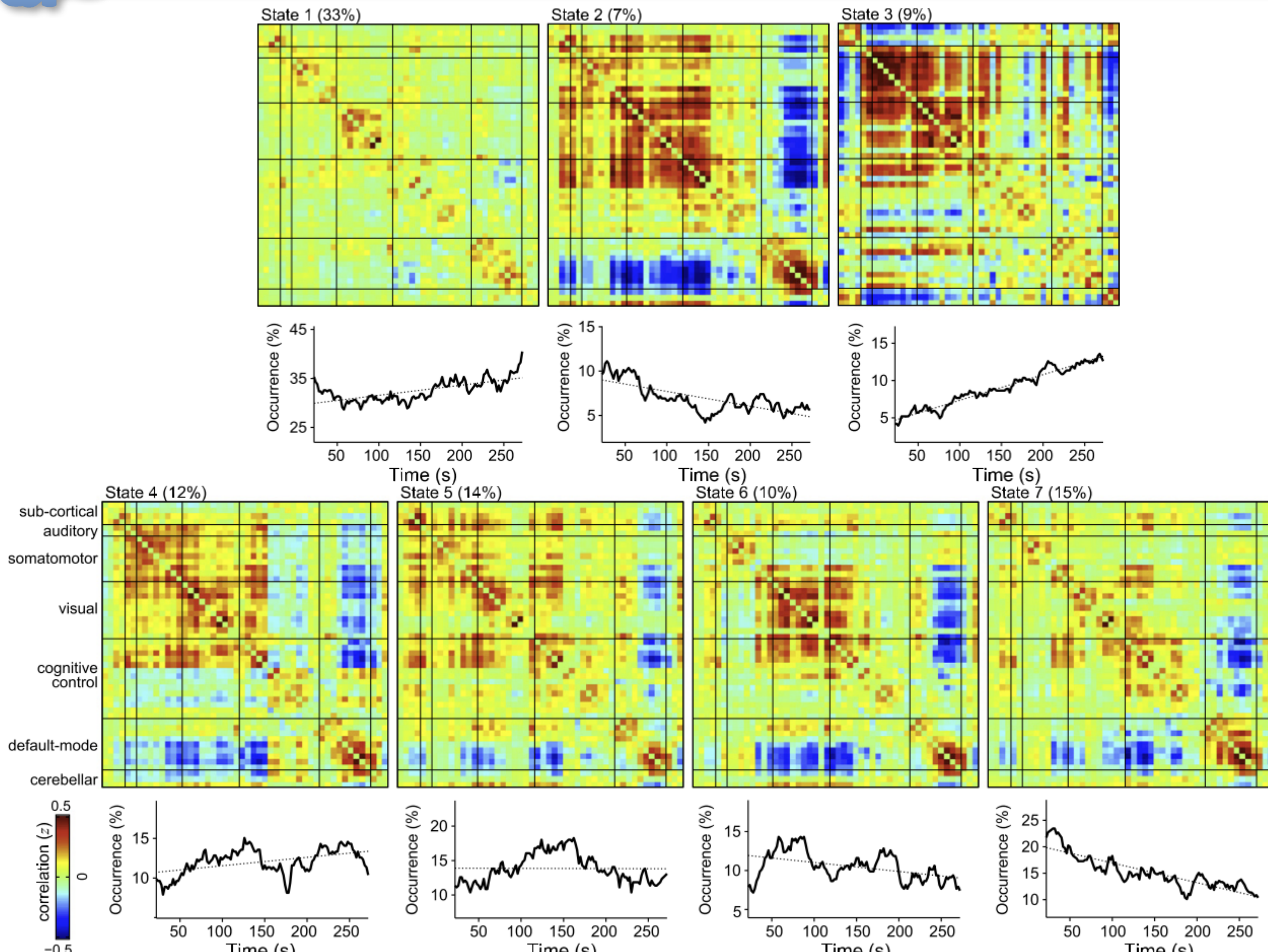
Shen et al. PNAS 2015

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



Allen et al. Cer. Cortex, 2014

Reproducible Short-term patterns of FC – Connectivity States



Allen et al.
Cer. Cortex, 2014

FC Dynamics – Interim Conclusions (I)

- 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.

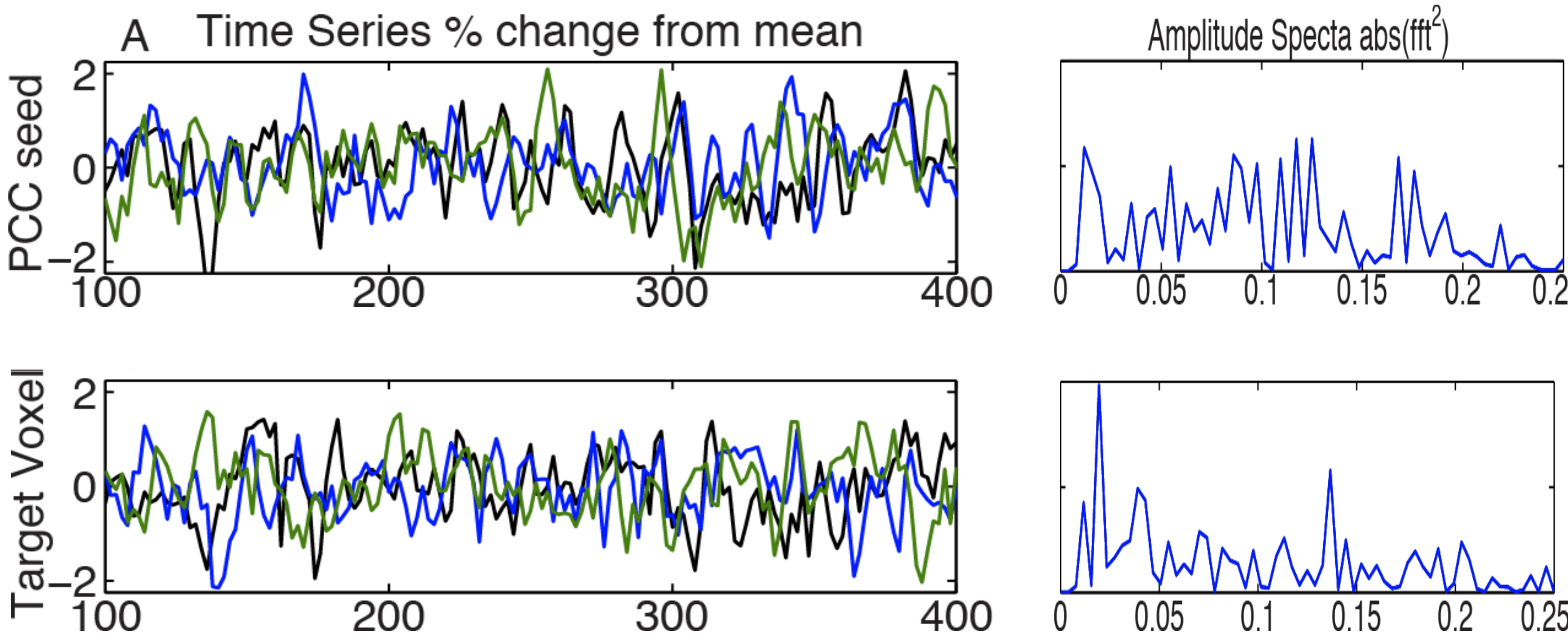
- FC Dynamics have well defined spatial patterns:
  - Interhemispheric Homotopic Connections are among the most stable.
  - Heterotopic Connections are among the most variable.

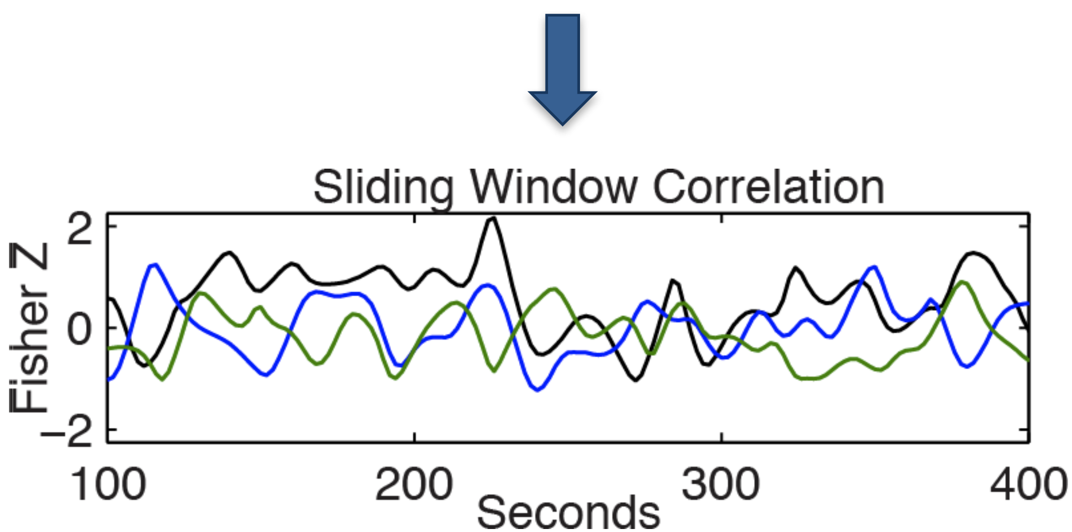
- Spatial distribution of FC Dynamics overlap with:
  - Spatial maps of Between-Subject Long Term FC Stability.
  - Spatial maps of evolutionary cortical expansion.

- There are reproducible re-ocurring 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

Word of Caution



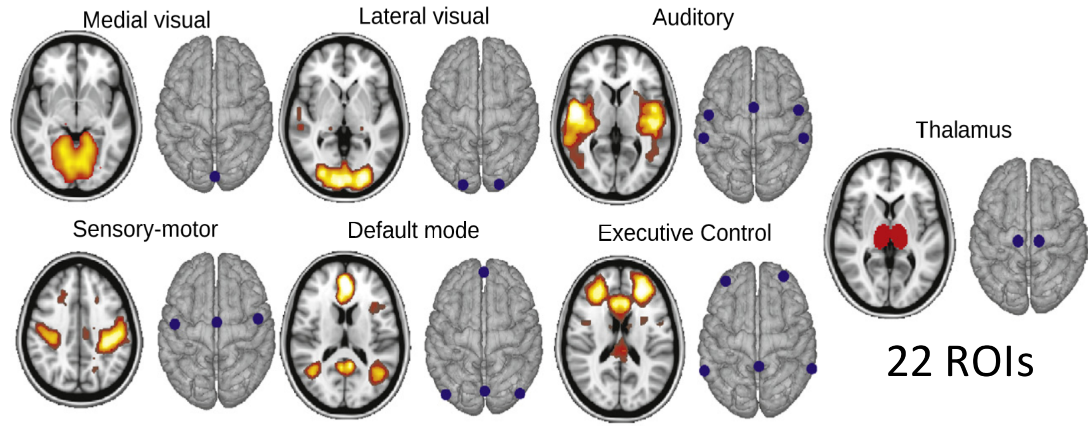


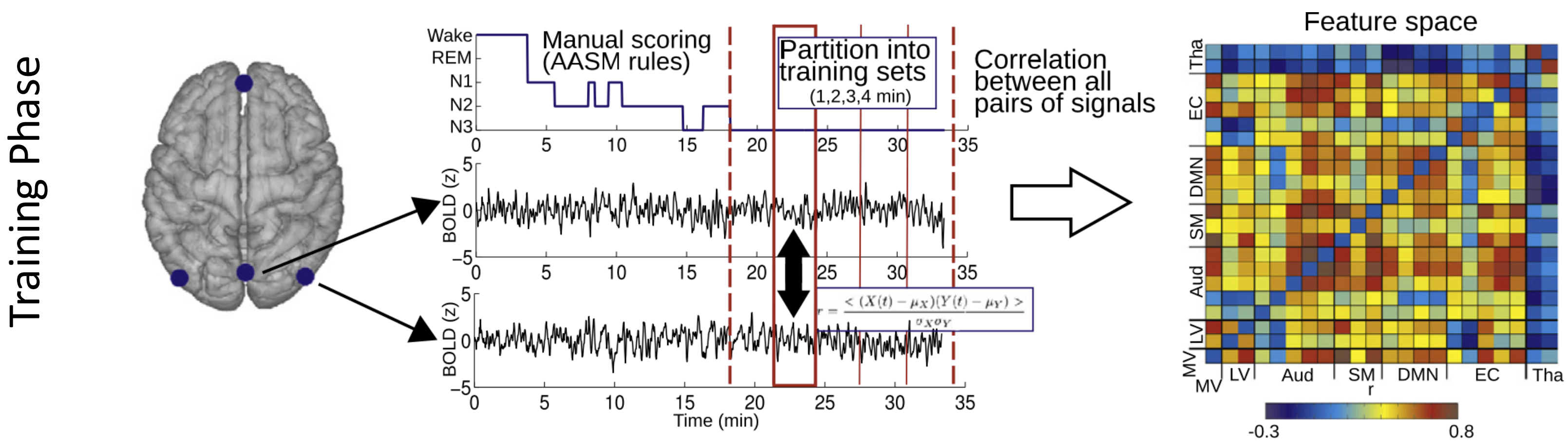
Regardless of whether or not there are neuronal interactions, two random time-series can show sliding window correlation dynamics.

Handwerker et al. NeuroImage 2012

FC Dynamics vs. Sleep Stages

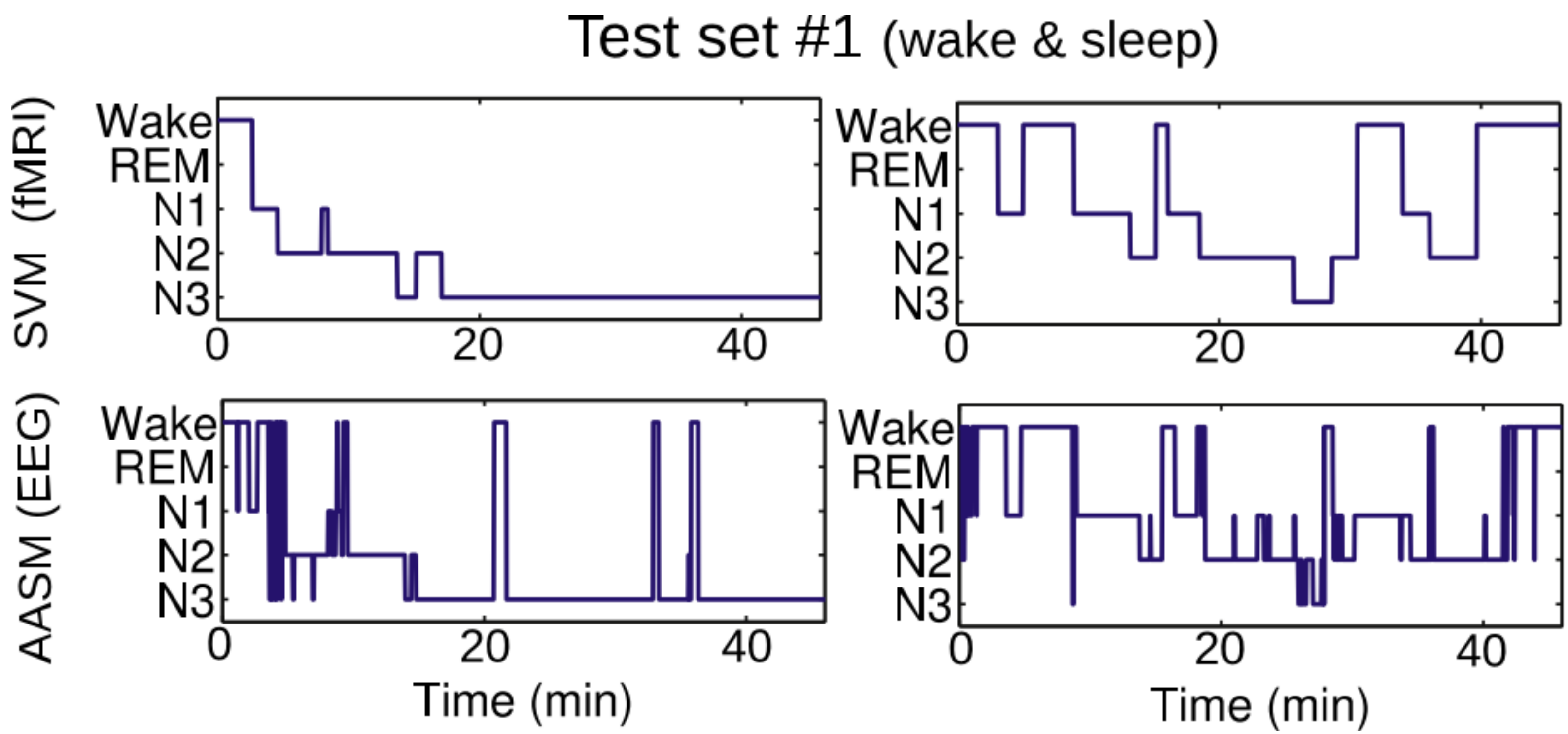
- Concurrent BOLD fMRI and EEG Recordings.
- Approx. 50 min long scans.
- Manual Sleep Staging based on EEG/AASM Criteria.
- WL = 60 s – 4 minutes





Algorithm: Multi-level Support Vector Machine

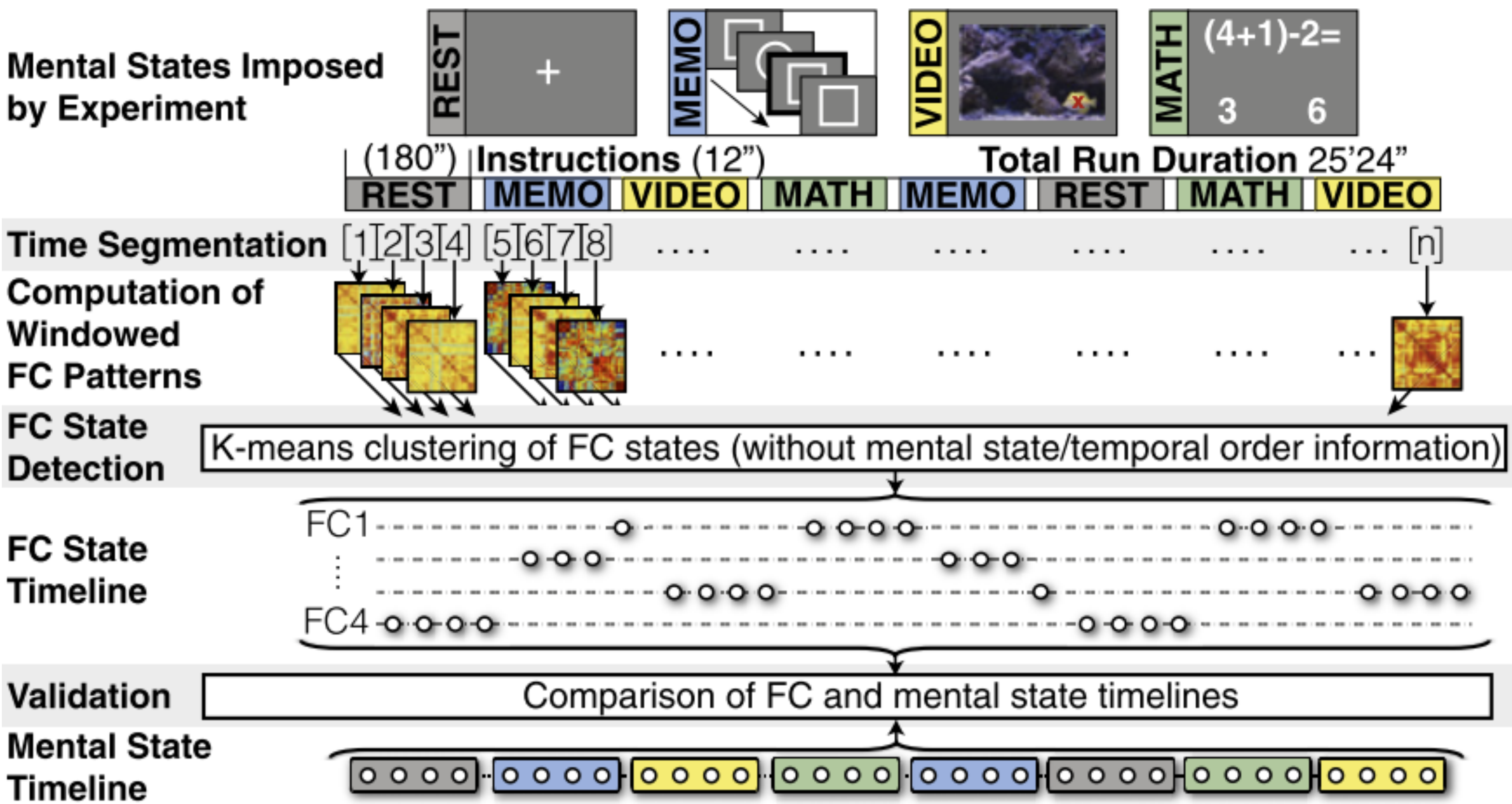
Tagliazucchi et al. NeuroImage 2012



80% Accuracy for WL = 2 mins and above

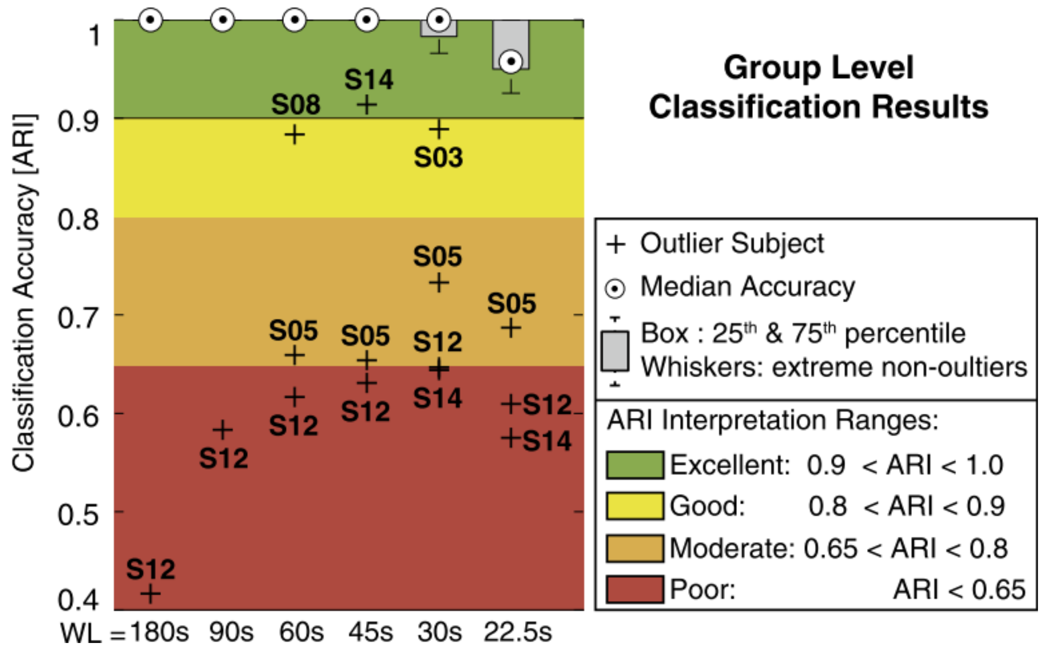
Tagliazucchi et al. NeuroImage 2012

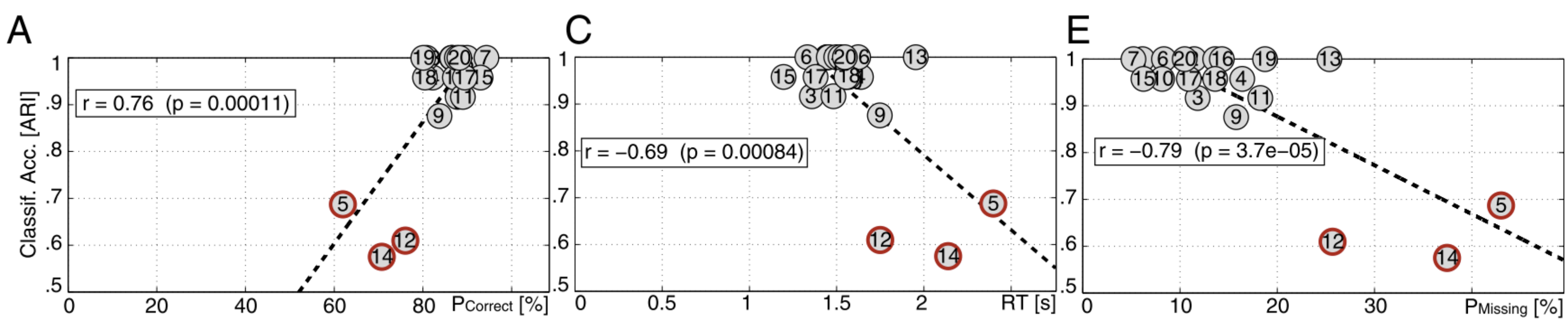
FC Dynamics vs. Mental States Imposed by Task (I)



Gonzalez-Castillo et al. PNAS 2015

FC Dynamics vs. Mental States Imposed by Task (II)

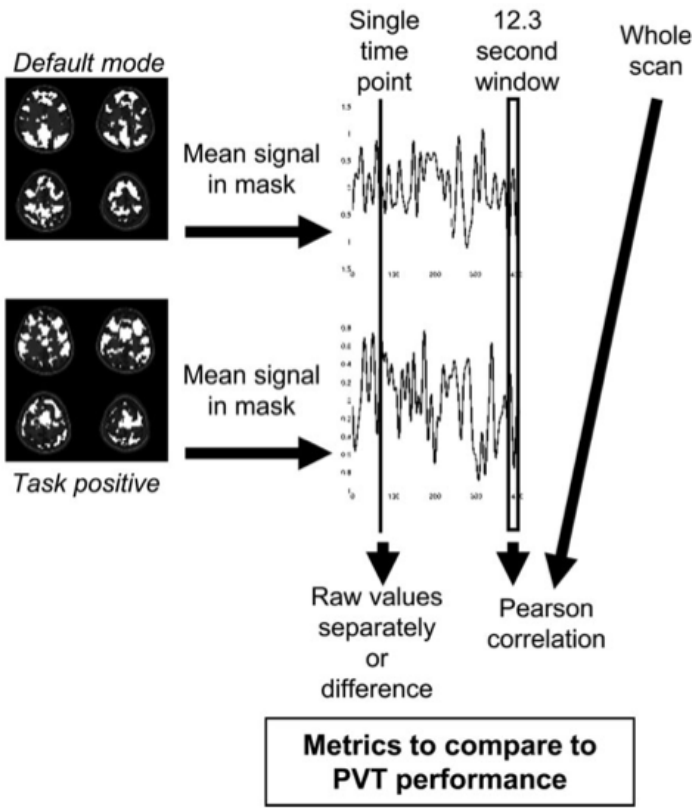




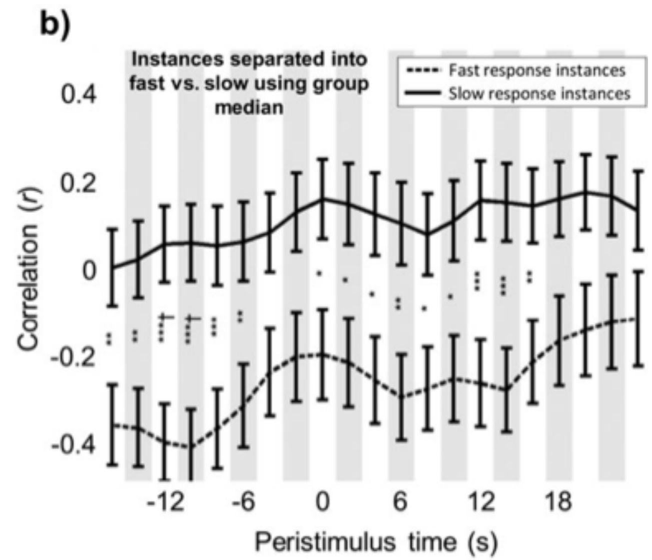
Gonzalez-Castillo et al. PNAS 2015

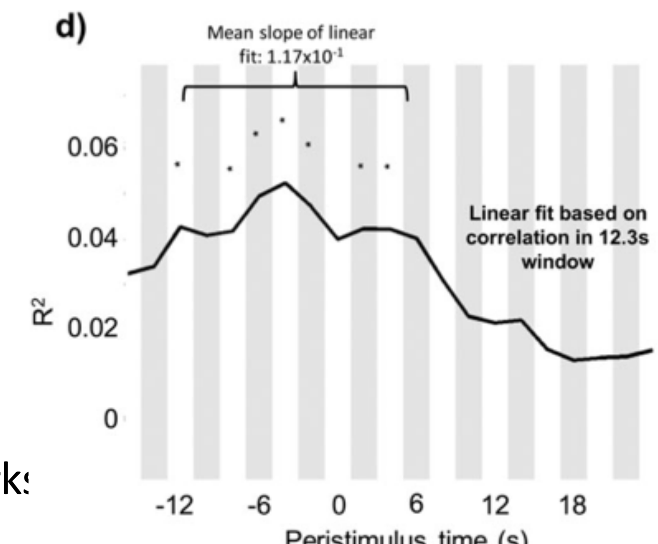
FC Dynamics vs. Task Outcome Prediction

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



TR = 300ms

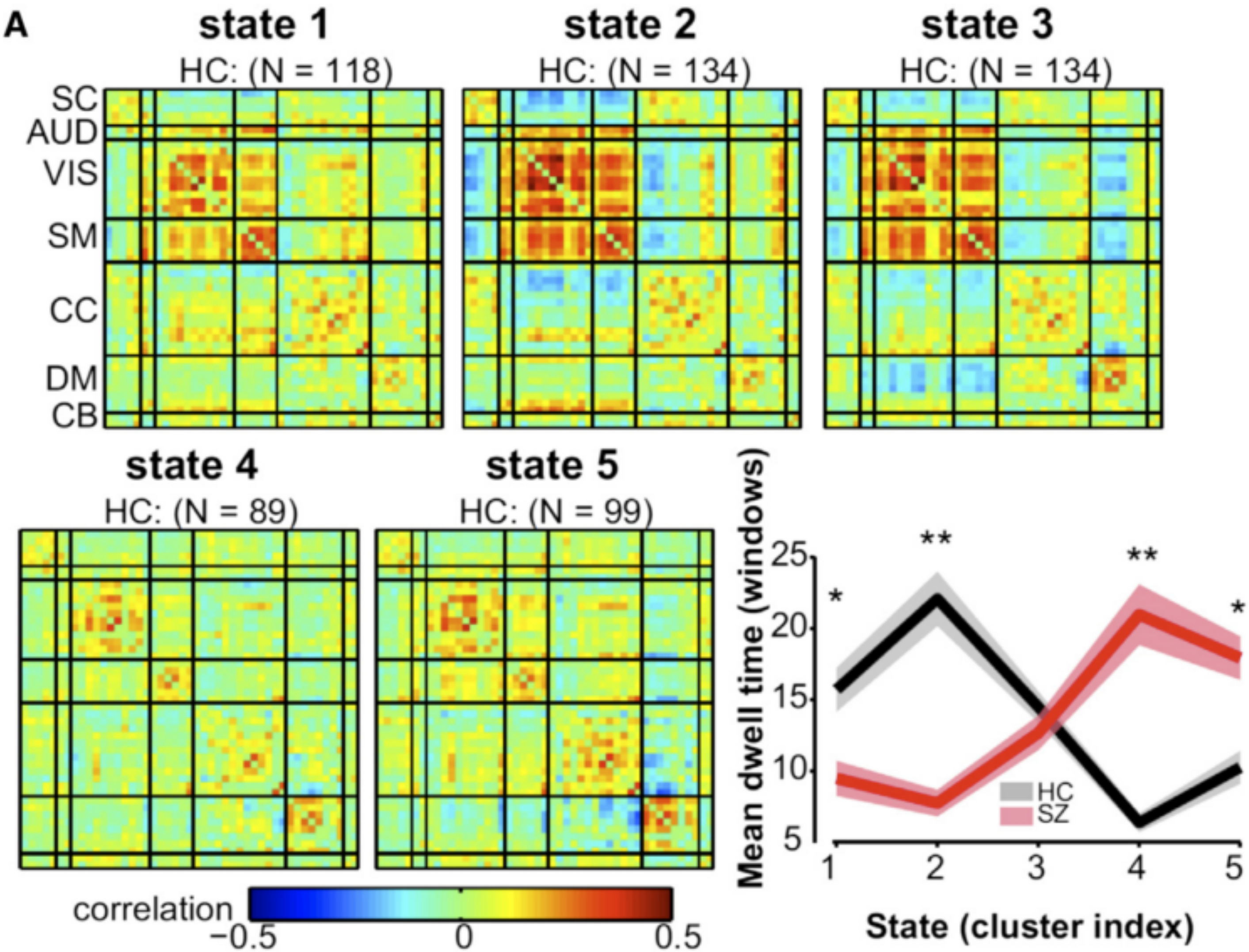




In most cases, more anti-correlation between networks was significantly related to faster performance.

Thompson et al. Human Brain Mapping 2013

Alterations of Dynamic Connectivity & Disease (I): Schizophrenia



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.

Damaraju et al. NeuroImage Clinical, 2014

Interim Conclusions (II)

- **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

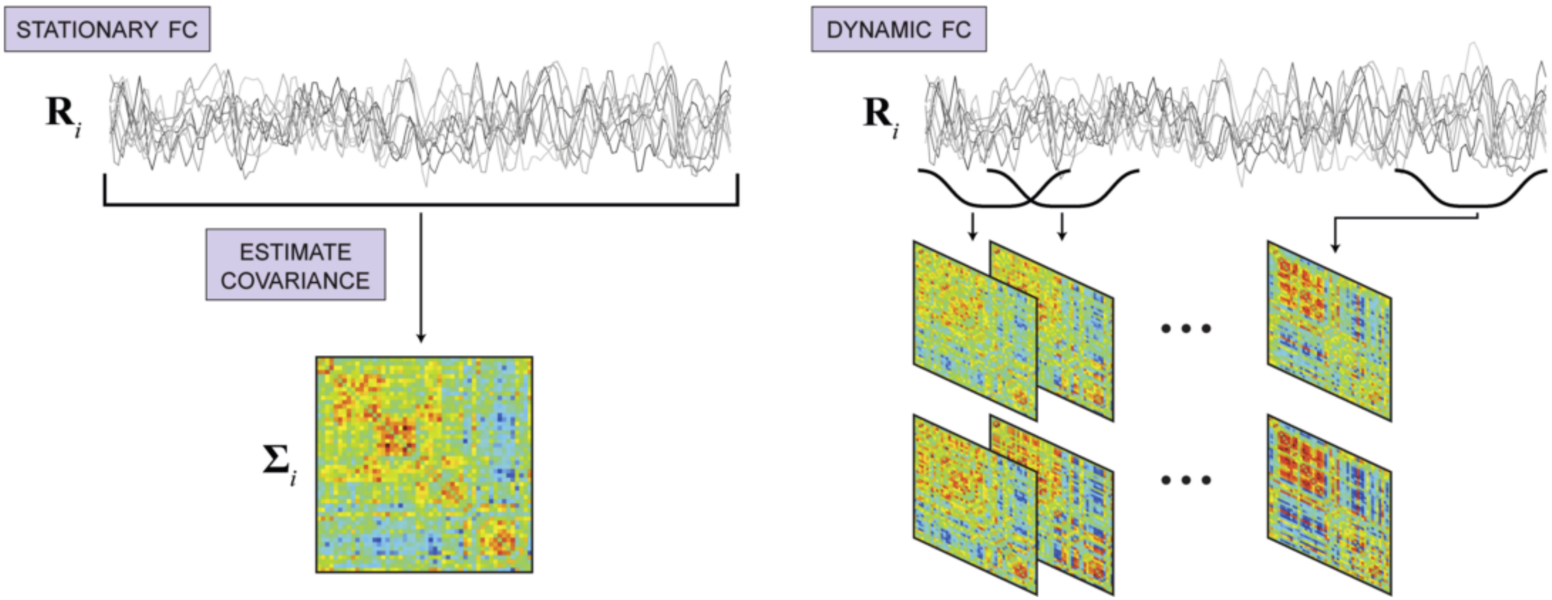
- **Comparison / Consolidation of Results is quite challenging.**

- **Some groups already working on potential clinical applications based on measures of dynamic FC**
  - Schizophrenia, Bipolar Disorder, Alzheimer's, Multiple Sclerosis…

SOME METHODOLOGICAL CONSIDERATIONS

Sliding Window Analysis

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.

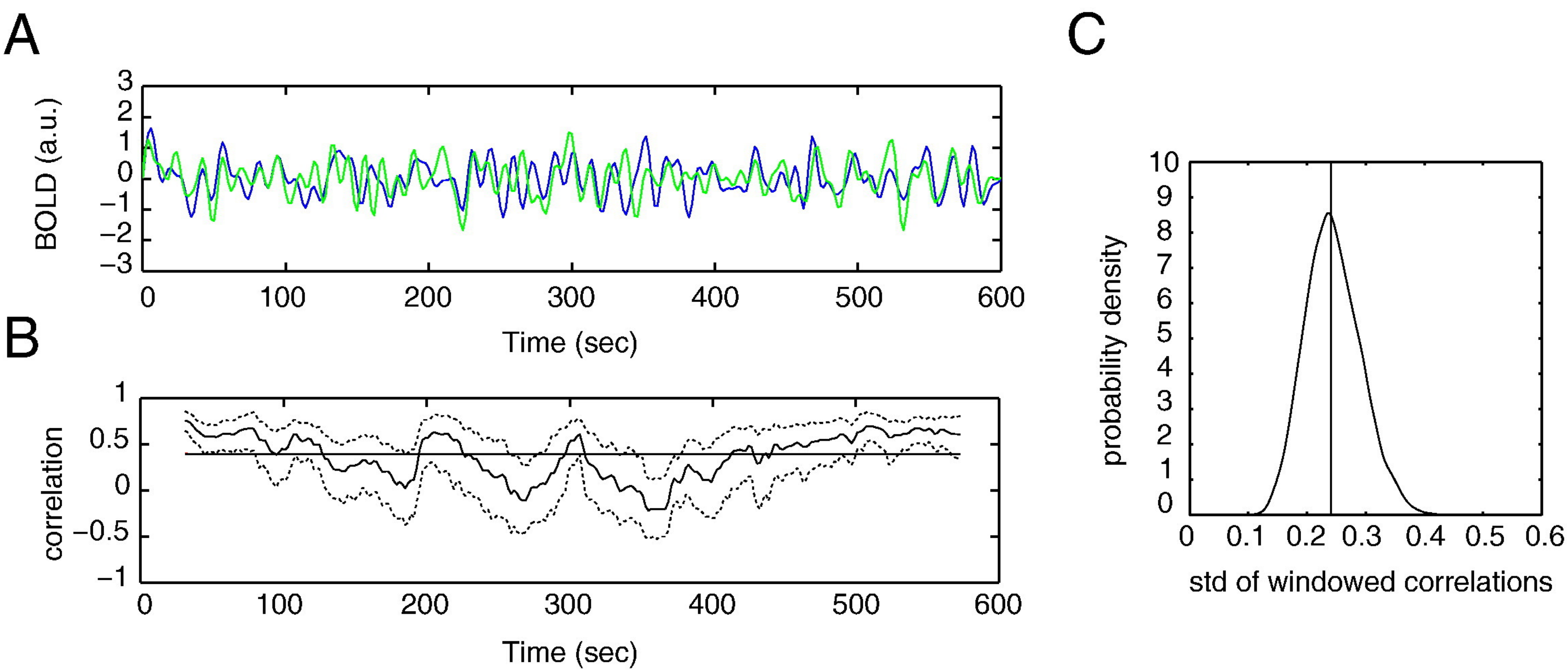
CONS:

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

Sliding Window Analysis

*"… pitfall is **to identify an observed value of a test statistic with its true underlying value**. This means that the mere presence of fluctuations in an observed FC time series is taken as evidence for the presence of dFC. The pitfall is that of overlooking the fact that the observed FC values are estimates of the true (and unobservable) values, and hence, are subject to statistical uncertainty…*

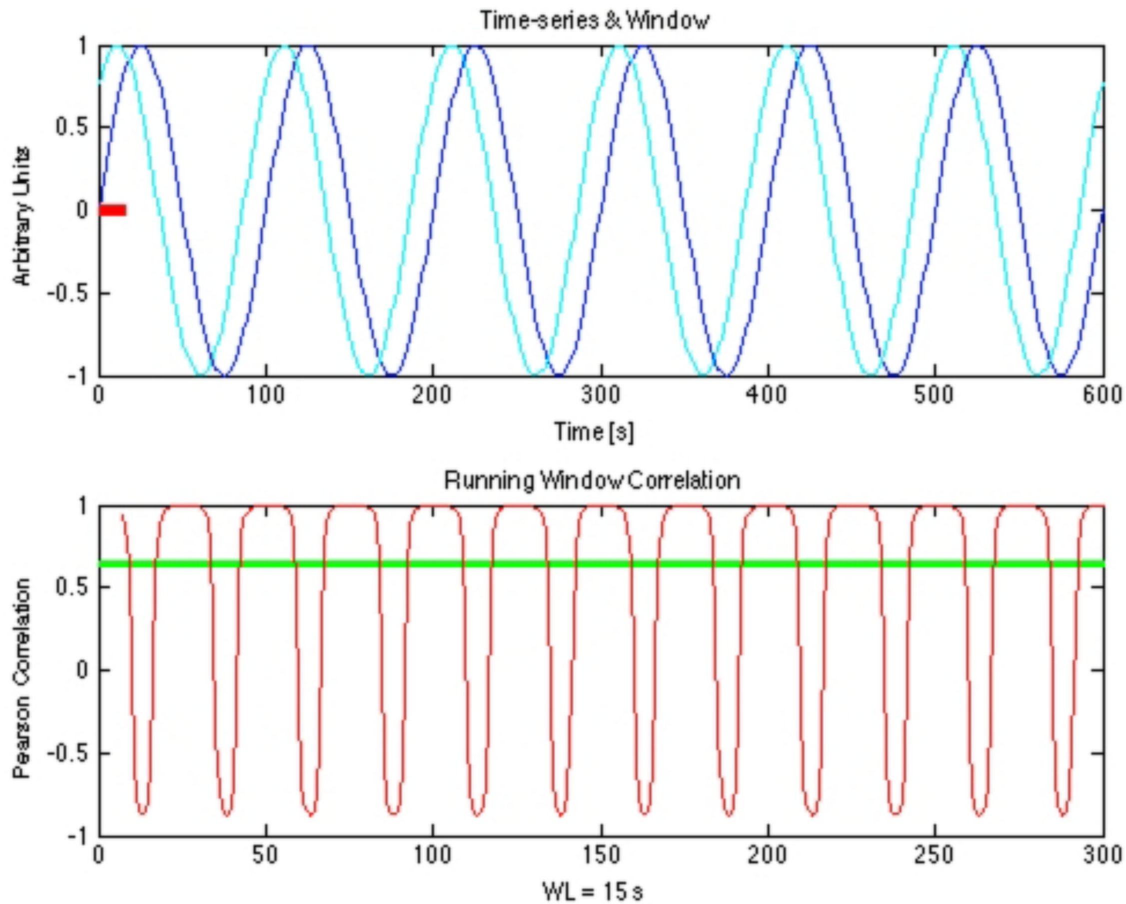
…Thus, to decide whether fluctuations in an observed FC time series are due to statistical uncertainty or reflect true changes in population FC, an appropriate statistical test has to be carried out."



Hindriks et al. NeuroImage 2016

Sliding Window Correlation: Spurious Correlations (I)

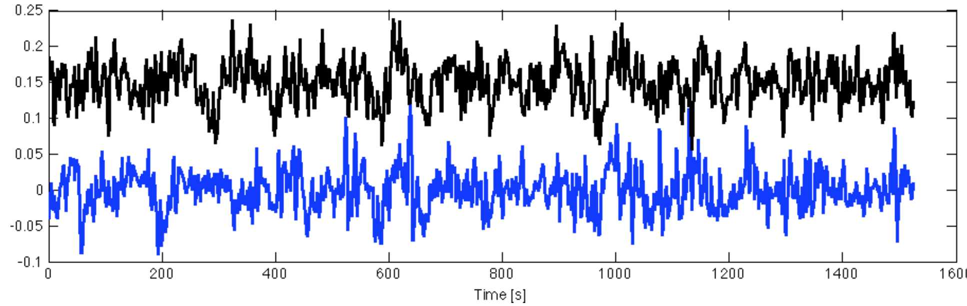
WL < 1 Period of slower fluctuation ➔ Spurious fluctuations in correlation traces will appear



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

Leonardi et al. NeuroImage 2015

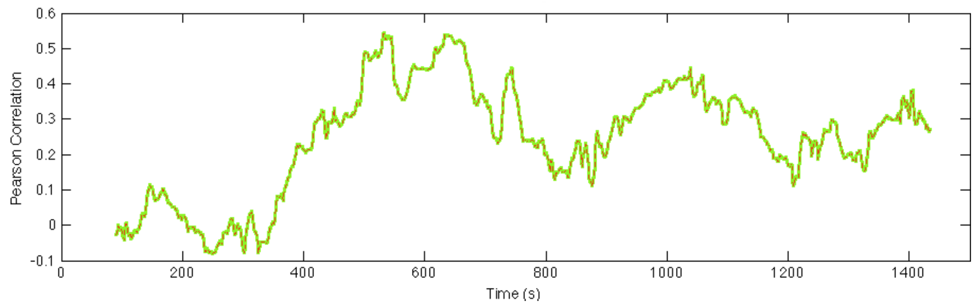
Sliding Window Correlation: Spurious Fluctuations (II)



Signal from 2 ROIs

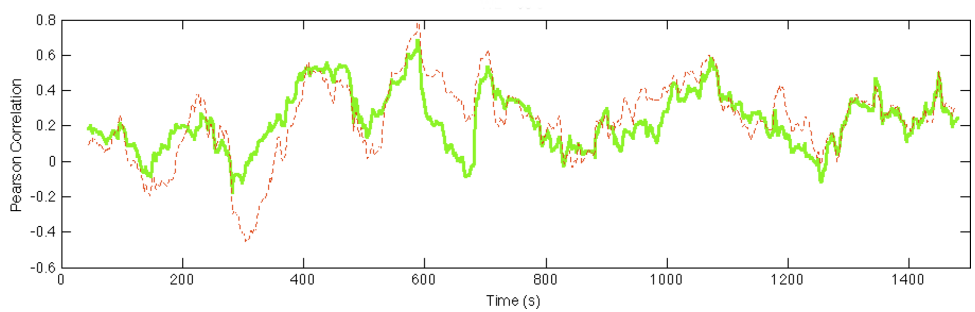
Time series of sliding window correlations between both ROIs

WL = 180s



0.006 – 0.18Hz

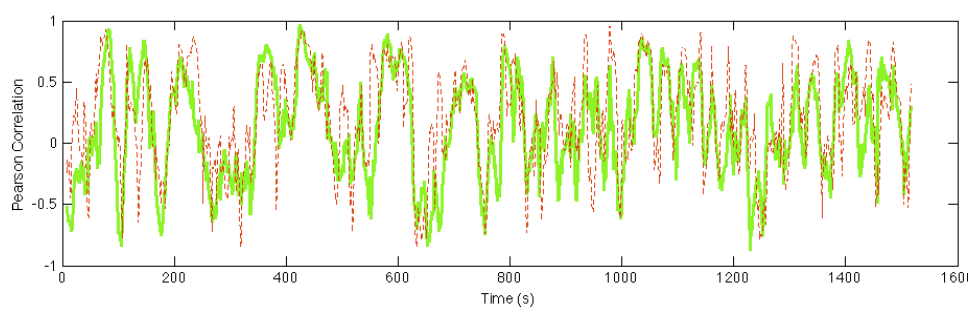
WL = 90s



0.011 – 0.18Hz

0.006 – 0.18Hz

WL = 15s

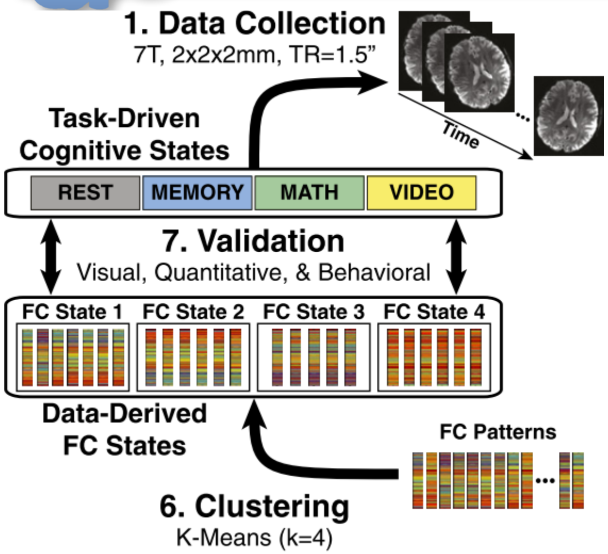


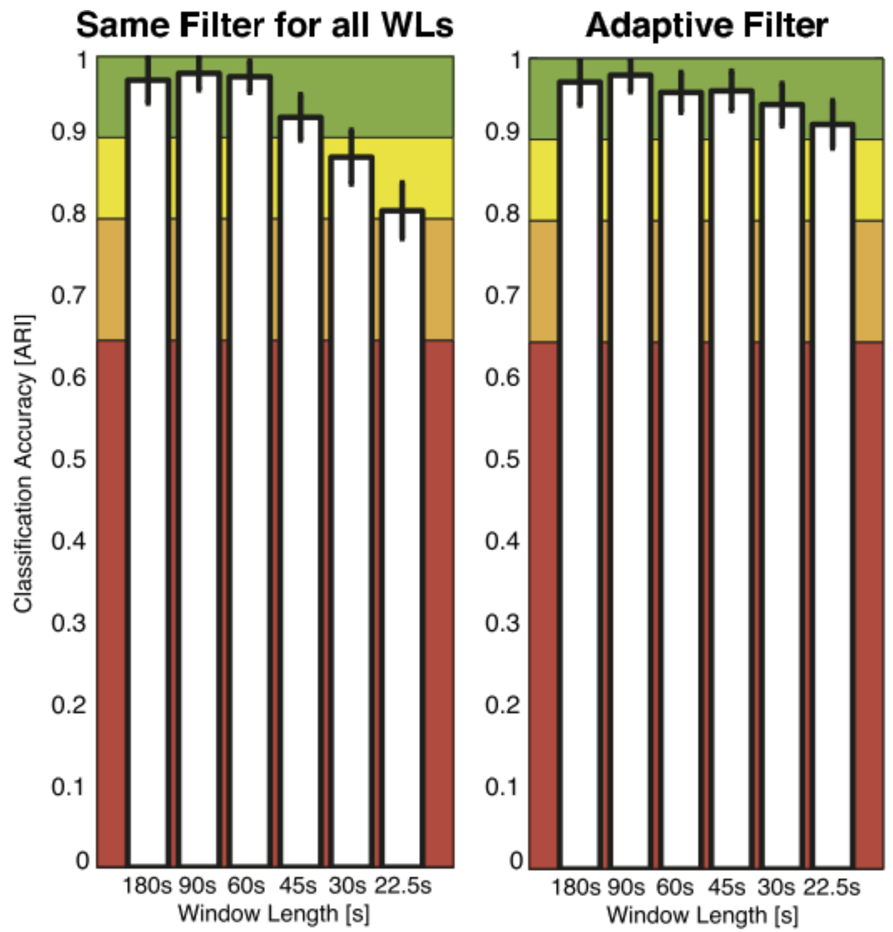
0.066 – 0.18Hz

0.006 – 0.18Hz

Leonardi et al. 2015

Sliding Window Correlation: Spurious Fluctuations (II)

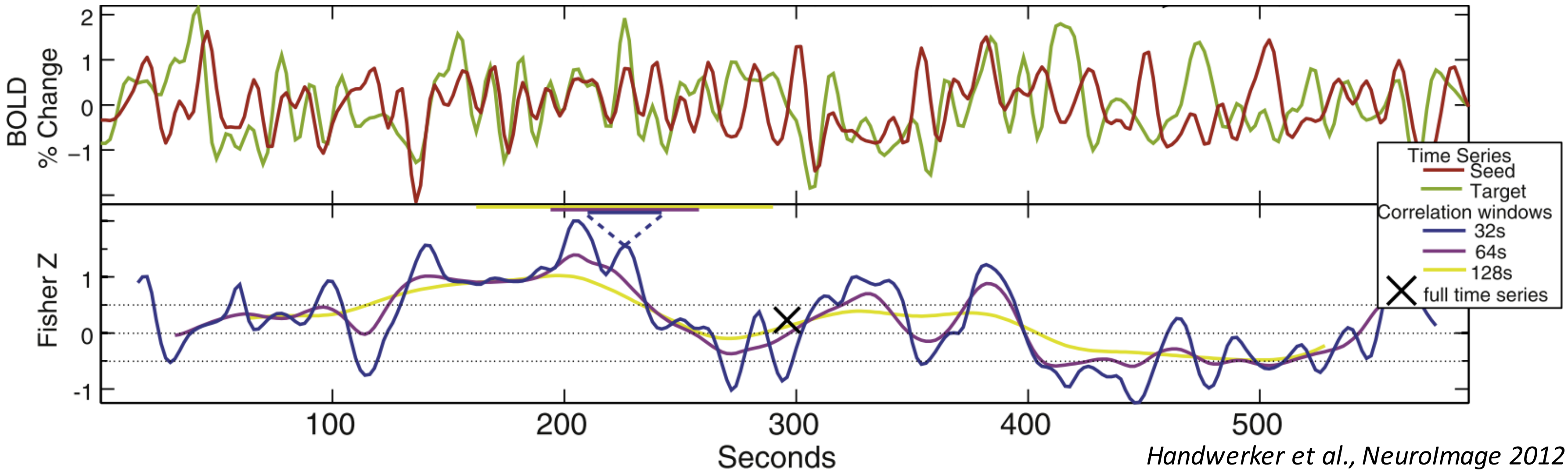




Gonzalez-Castillo et al., PNAS 2015

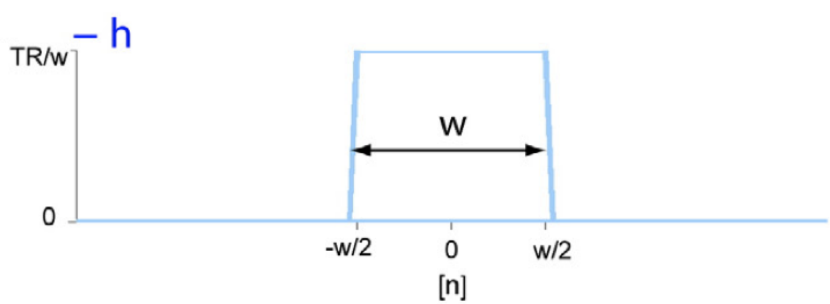
Sliding Window Correlation: Window Length vs. Amount of Fluctuation

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

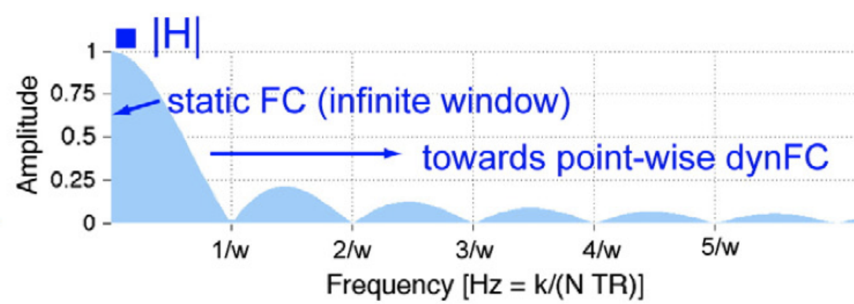


Handwerker et al., NeuroImage 2012

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



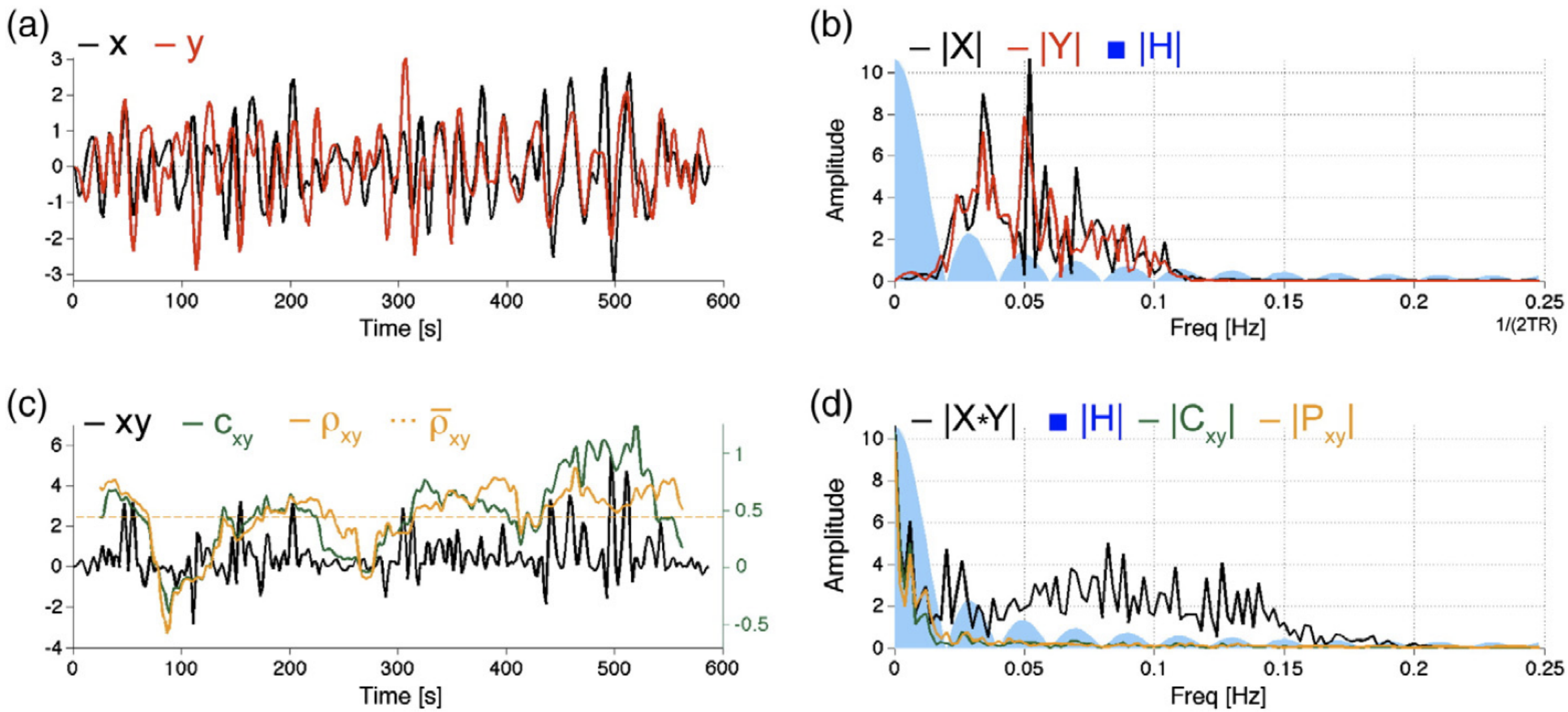
Window in Frequency Domain

Leonardi et al. NeuroImage, 2015

FIM

Sliding Window Correlation: Window Length vs. Amount of Fluctuation

WL = 50s ➔ $\text{Fmin}_{\text{signals}} = \text{Fmax}_{\text{observedDynamicConn}}$ = 0.02 Hz



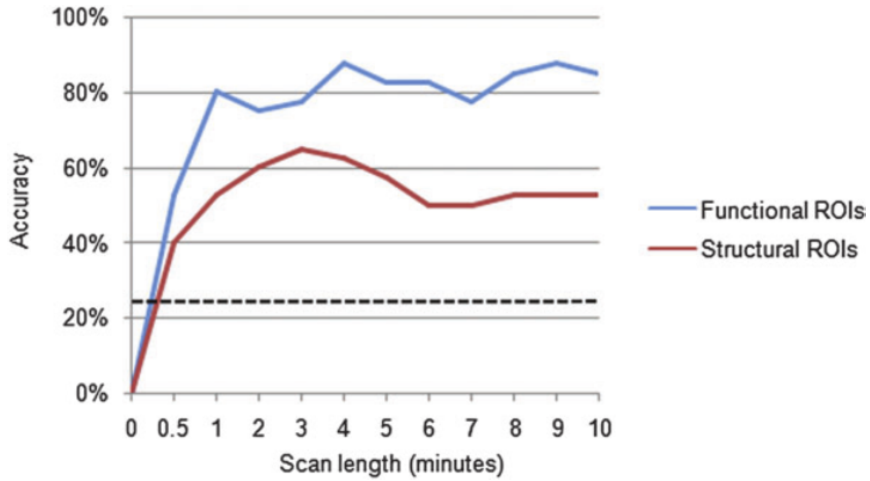
(1) Spurious fluctuations in dynFC can be limited by appropriate high pass filtering (1/WL).

(2) Remaining fluctuations in dynFC will be low-pass filtered (1/WL).

(3) Smaller windows and/or longer TR → greater influence of noise in estimation of dynFC.

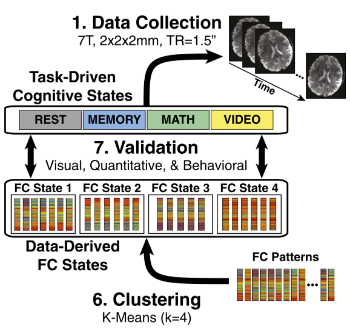
Leonardi et al. NeuroImage, 2015

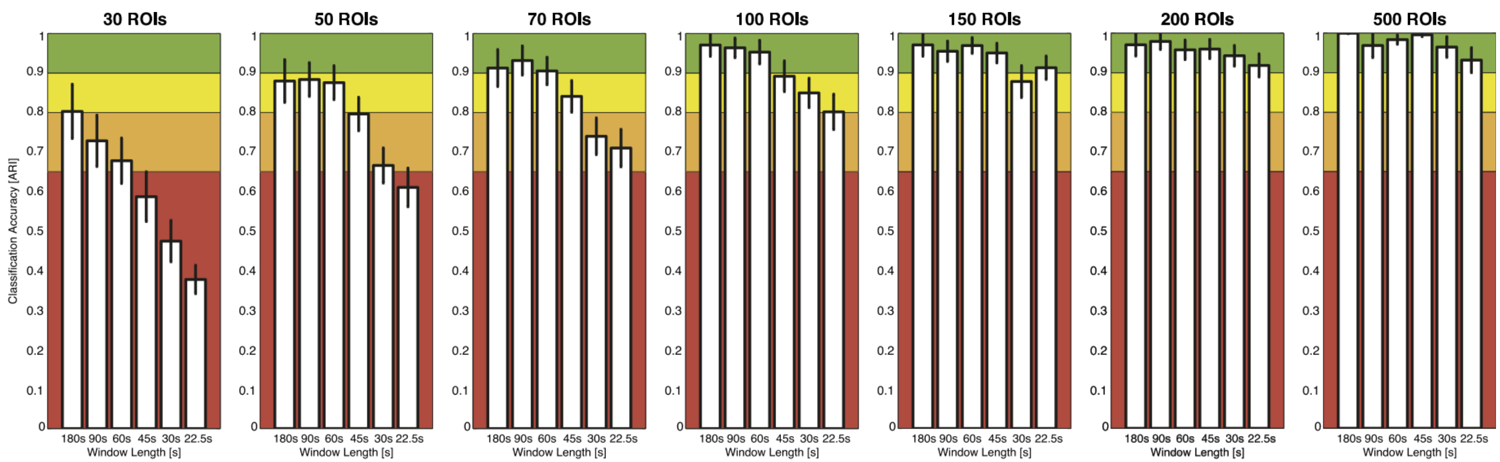
Functional Connectivity States: Parcellation Selection



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

Shirer et al. Cerebral Cortex 2012

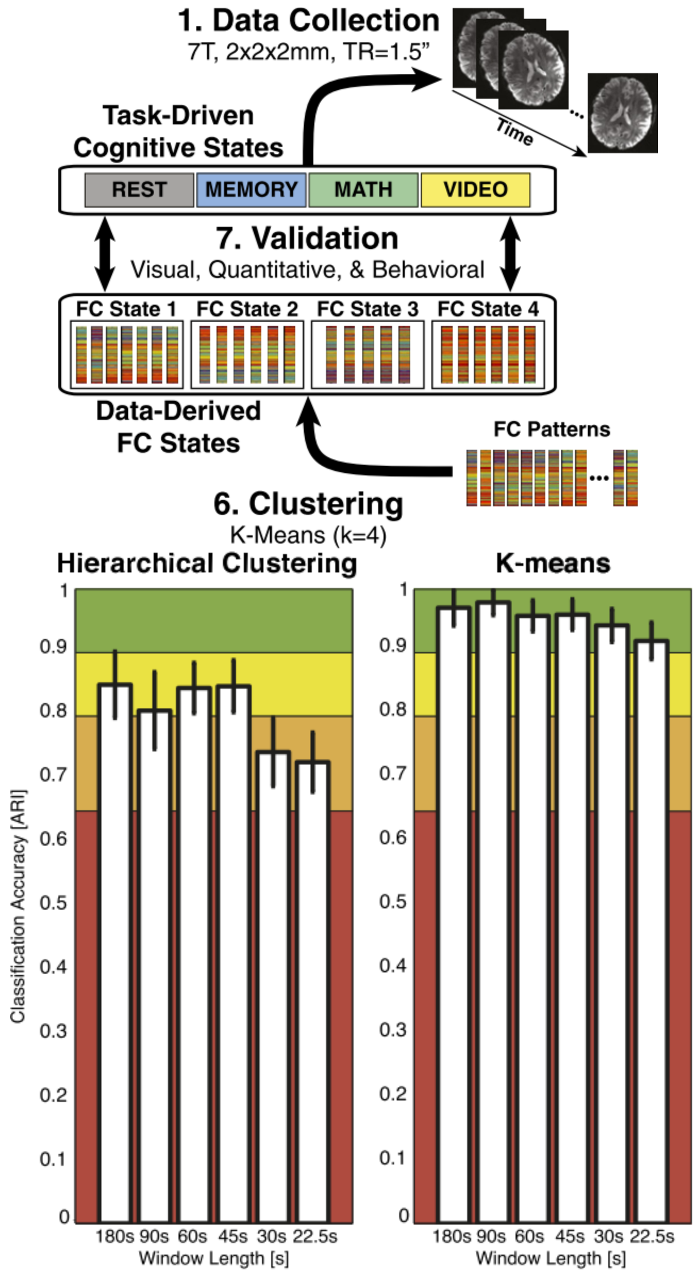




"More smaller ROIs" seem to perform better than "Less larger ROIS"

Gonzalez-Castillo et al., PNAS 2015

Functional Connectivity States: Clustering Algorithm



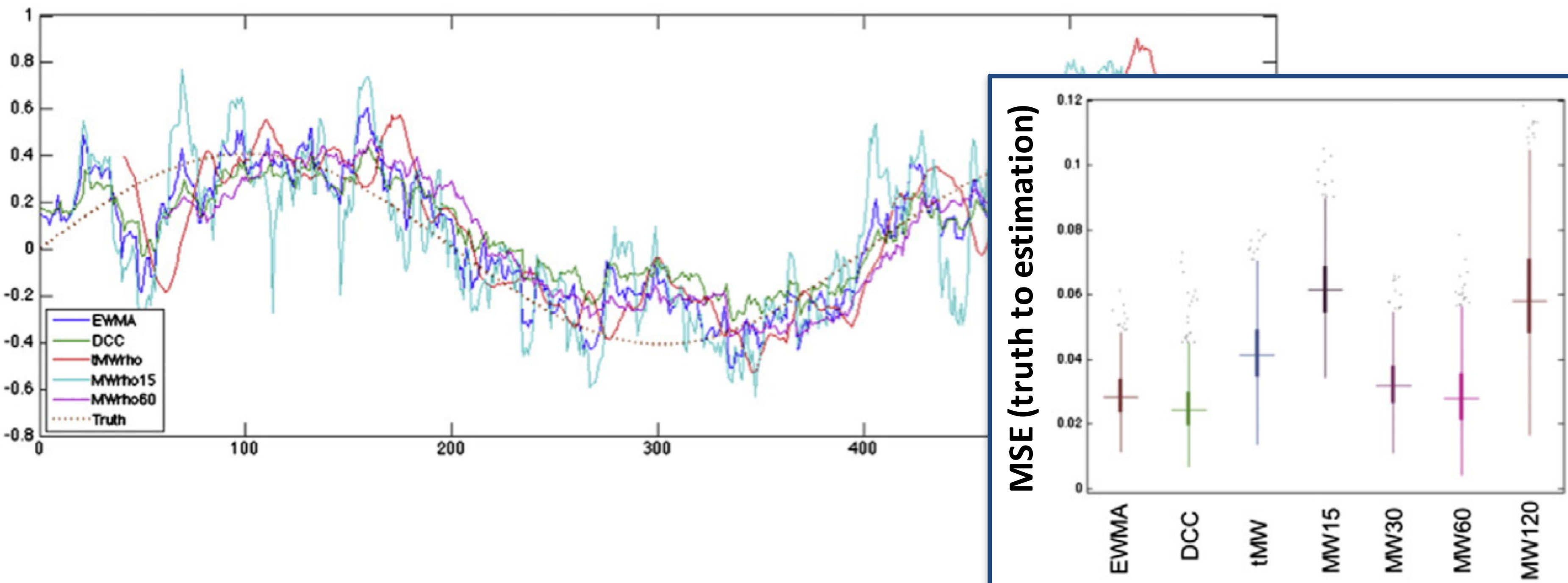
Gonzalez-Castillo et al., PNAS 2015

Other Methods: Dynamic Conditional Correlation (DCC) (I)

<u>DCC:</u> 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.

Slowly-varying Periodic change in correlation



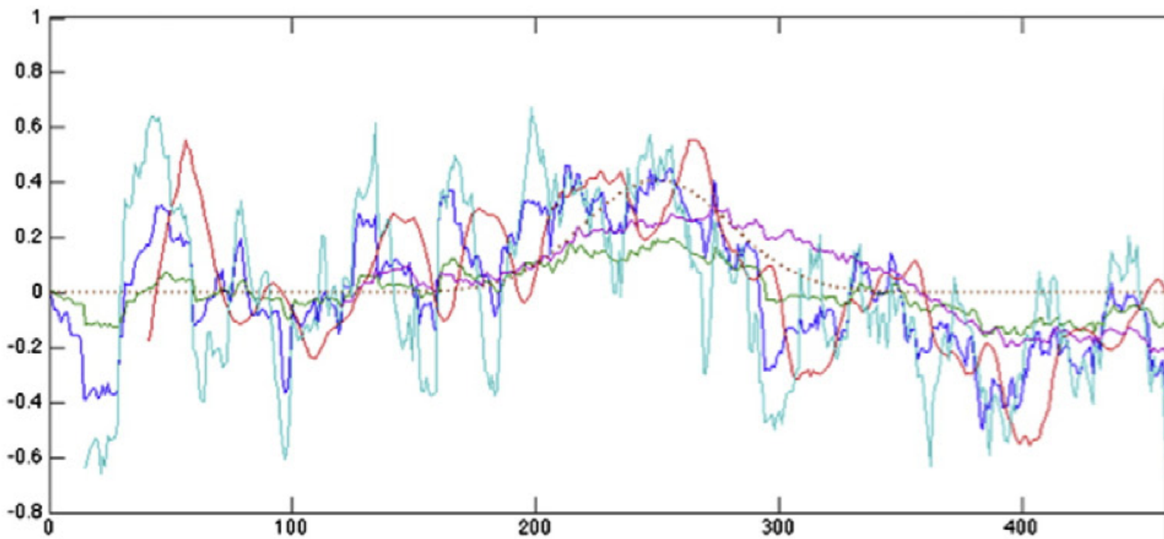
Linquist et al., NeuroImage, 2014

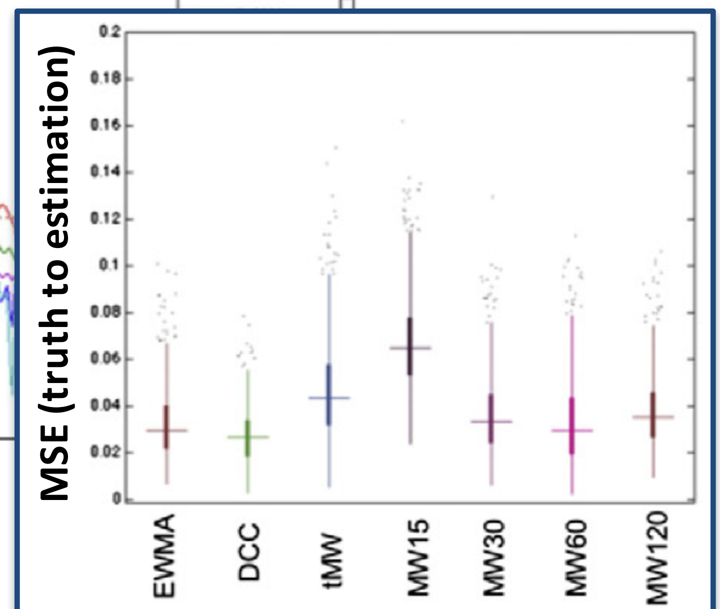
Other Methods: Dynamic Conditional Correlation (DCC) (II)

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.

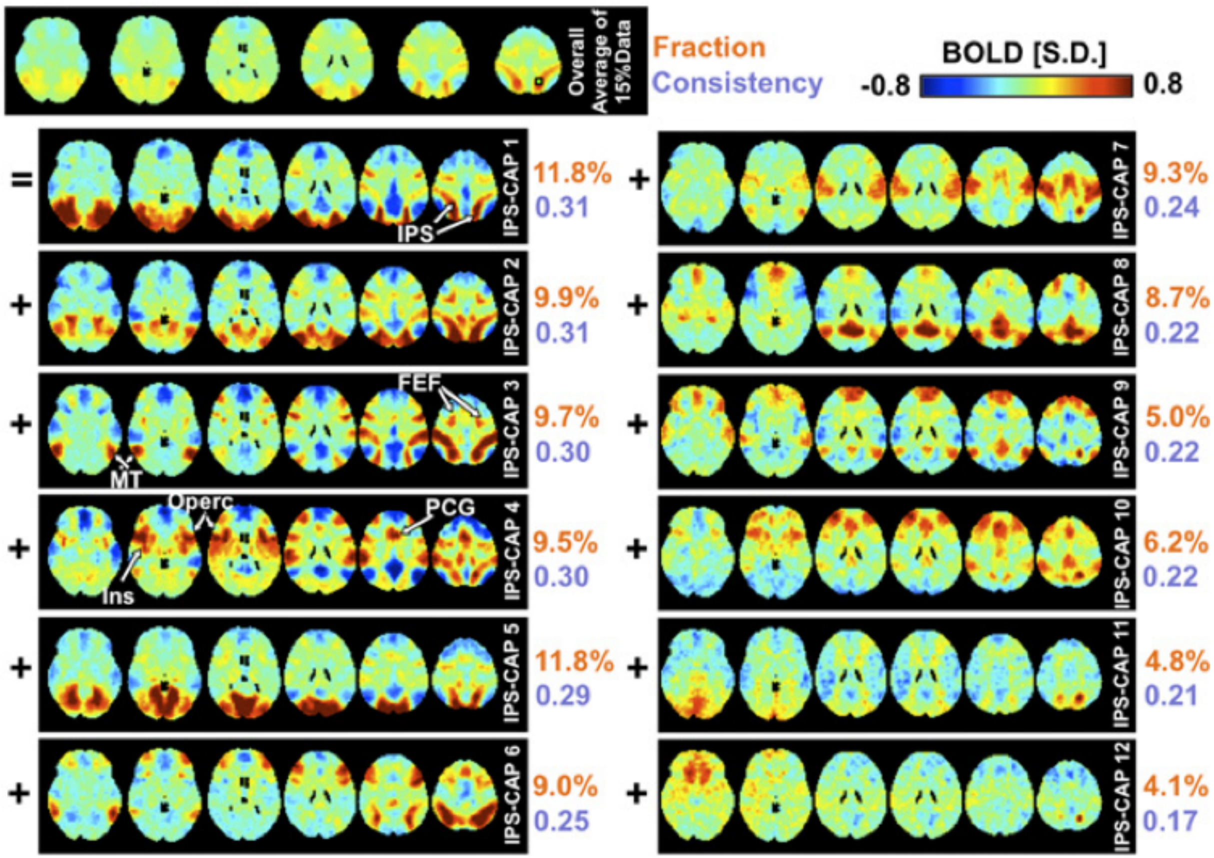
Linquist et al., NeuroImage, 2014

Other Methods (II): Co-Activation Patterns

❖ **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

General Conclusions / Open Questions

- 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.

Some Guidelines

❖ 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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Sean Marret
Vinai Roopchansingh
Souheil Inati
Andy Derbishire

FMRIF
fmrif.nimh.nih.gov