Dynamic Resting State fMRI

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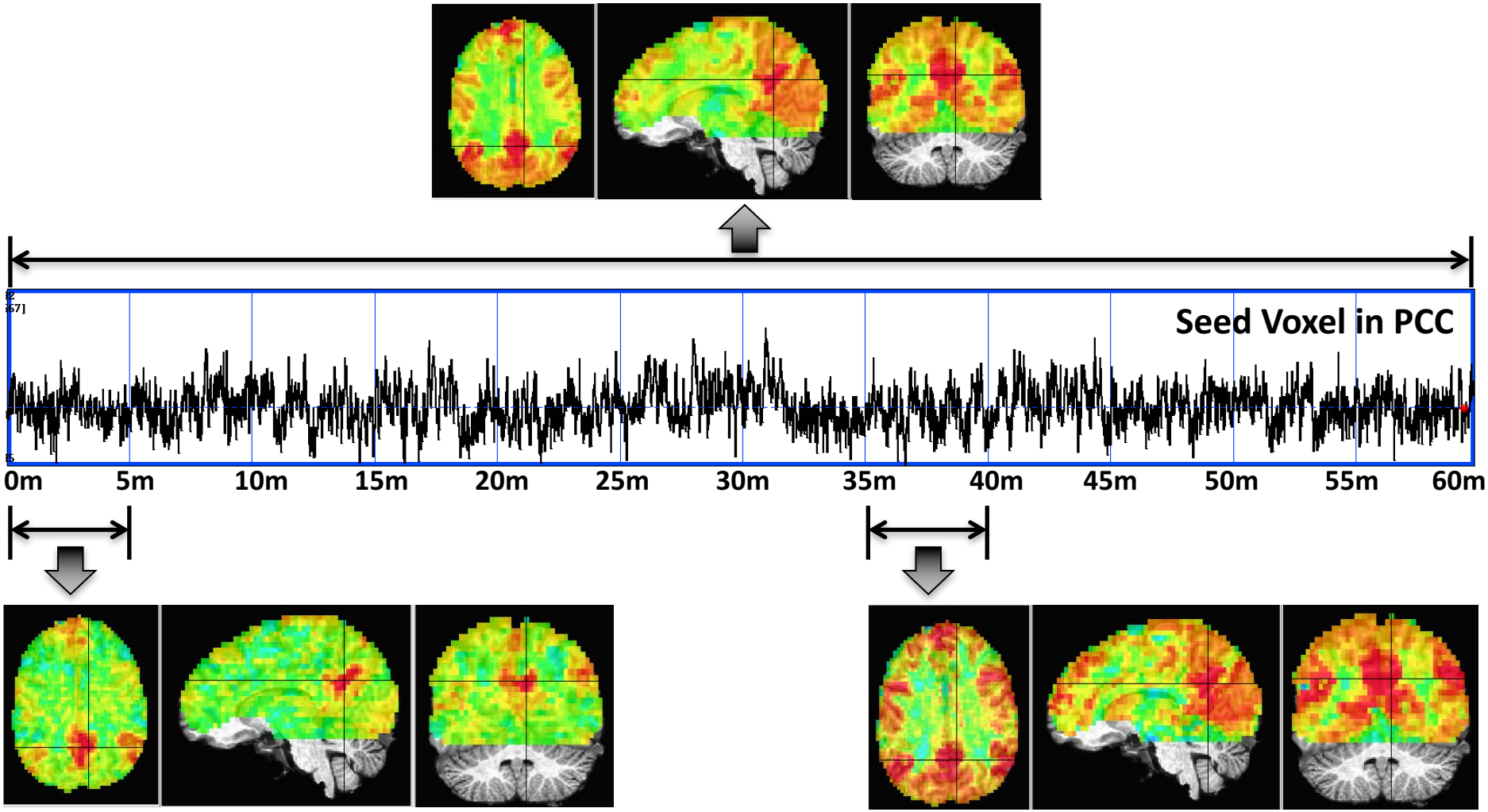
Agenda

- **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)
  - Dynamic Connectivity Detection (DCD)
  - Single-volume Co-Activation Patterns (CAPs)
  - Others…
- **CONCLUSIONS**

fMRI Connectivity Dynamics: DEFINITION



60 Minutes of Continuous Rest Data | TR = 1s

Where to go next…

REVIEW ARTICLES

NeuroImage

Volume 80, 15 October 2013, Pages 360–378

Dynamic functional connectivity: Promise, issues, and interpretations

R. Matthew Hutchison[a], [1], Thilo Womelsdorf[b], Elen…
Calhoun[d, f], Maurizio Corbetta[g, h], Stefania Della Penna[g], …

Neuron

Volume 84, Issue 2, 22 October 2014, Pages 262-274

Perspective

The Chronnectome: Time-Varying Connectivity Networks as the Next Frontier in fMRI Data Discovery

Vince D. Calhoun [1, 2], Robyn Miller [1], Godfrey Pearlson [4], Tulay Adalı [3]

NeuroImage

Available online 26 December 2016

In Press, Corrected Proof

The dynamic functional connectome: State-of-the-art and perspectives

Maria Giulia Preti [a, b], [1], Thomas AW Bolton [a, b, 1], Dimitri Van De Ville [a, b]

Where to go next…

UPCOMING NEUROIMAGE SPECIAL ISSUE ON DYNAMIC CONNECTIVITY

NeuroImage

Available online 20 June 2017

In Press, Corrected Proof

Modeling and interpreting mesoscale network dynamics

Ankit N. Khambhati [a, b], Ann E. Sizemore [a], Richard F. Betzel [a], Danielle S. Bassett [a, b, c]

NeuroImage

Available online 29 June 2017

In Press, Corrected Proof

Discovering dynamic brain networks from big data in rest and task

Diego Vidaurre [a], Romesh Abeysuriya [a], Robert Becker [a], Andrew J. Quinn [a], Fidel Alfaro-Almagro [b], Stephen M. Smith [a], Mark W. Woolrich [a, b]

NeuroImage

Available online 8 July 2017

In Press, Corrected Proof

Dynamic graph metrics: Tutorial, toolbox, and tale

Ann E. Sizemore [a], Danielle S. Bassett [a, b]

NeuroImage

Available online 3 July 2017

In Press, Corrected Proof

Just a thought: How mind-wandering is represented in dynamic brain connectivity

Aaron Kucyi

NeuroImage

Available online 23 May 2017

In Press, Corrected Proof

Whole-brain connectivity dynamics reflect both task-specific and individual-specific modulation: A multitask study

Hua Xie [a, d], Vince D. Calhoun [b, c], Javier Gonzalez-Castillo [d], Eswar Damaraju [b, c], Robyn Miller [b], Peter A. Bandettini [d, e], Sunanda Mitra [a]

NeuroImage

Available online 3 August 2017

In Press, Corrected Proof — Note to users

Principles of dynamic network reconfiguration across diverse brain states

James M. Shine[a, b], Russell A. Poldrack[a]

NeuroImage

Available online 3 August 2017

In Press, Corrected Proof — Note to users

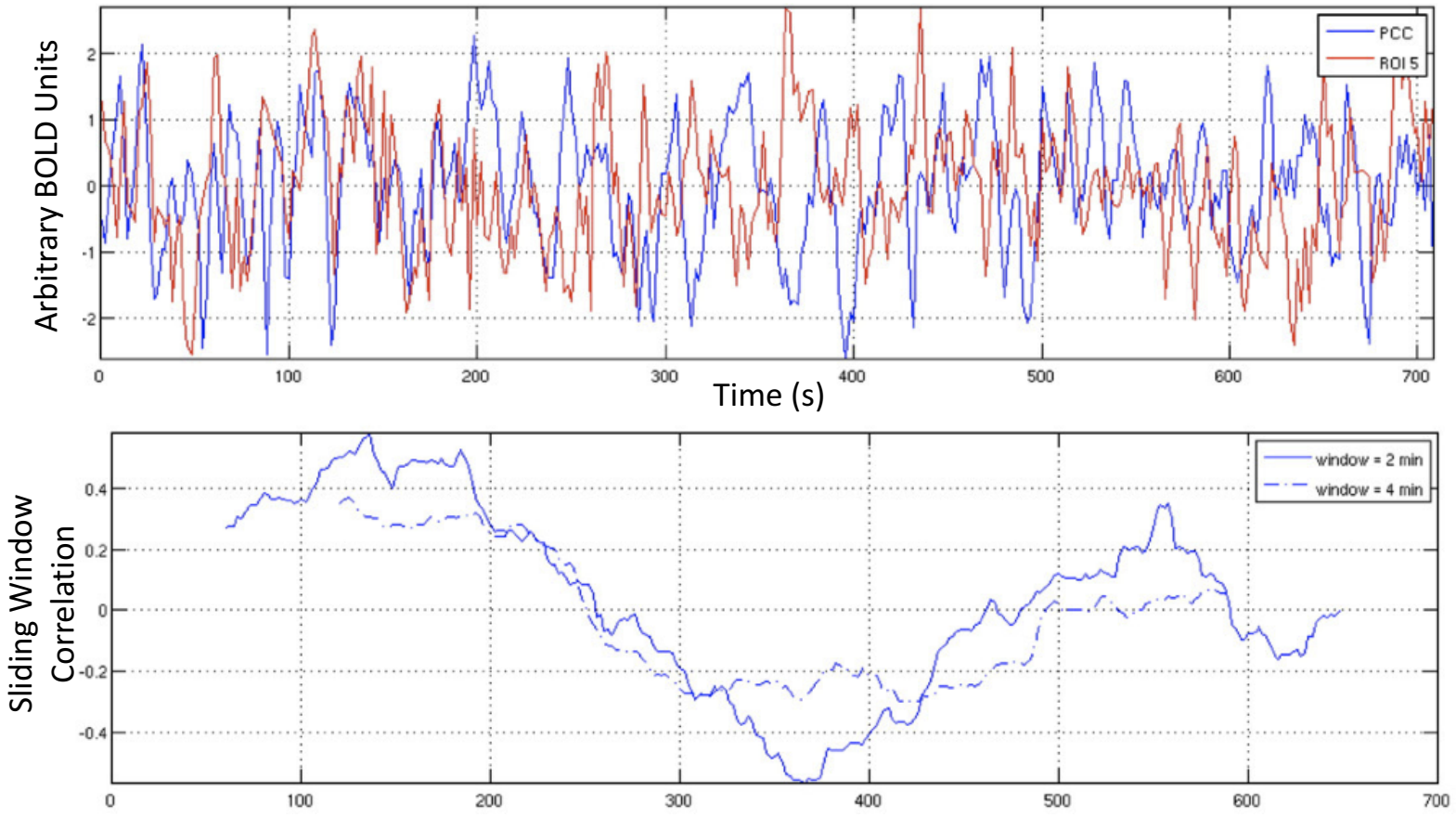
Task-based dynamic functional connectivity: Recent findings and open questions

Javier Gonzalez-Castillo[a], Peter A. Bandettini[a, b]

More will become available soon…

Original Observations (I)

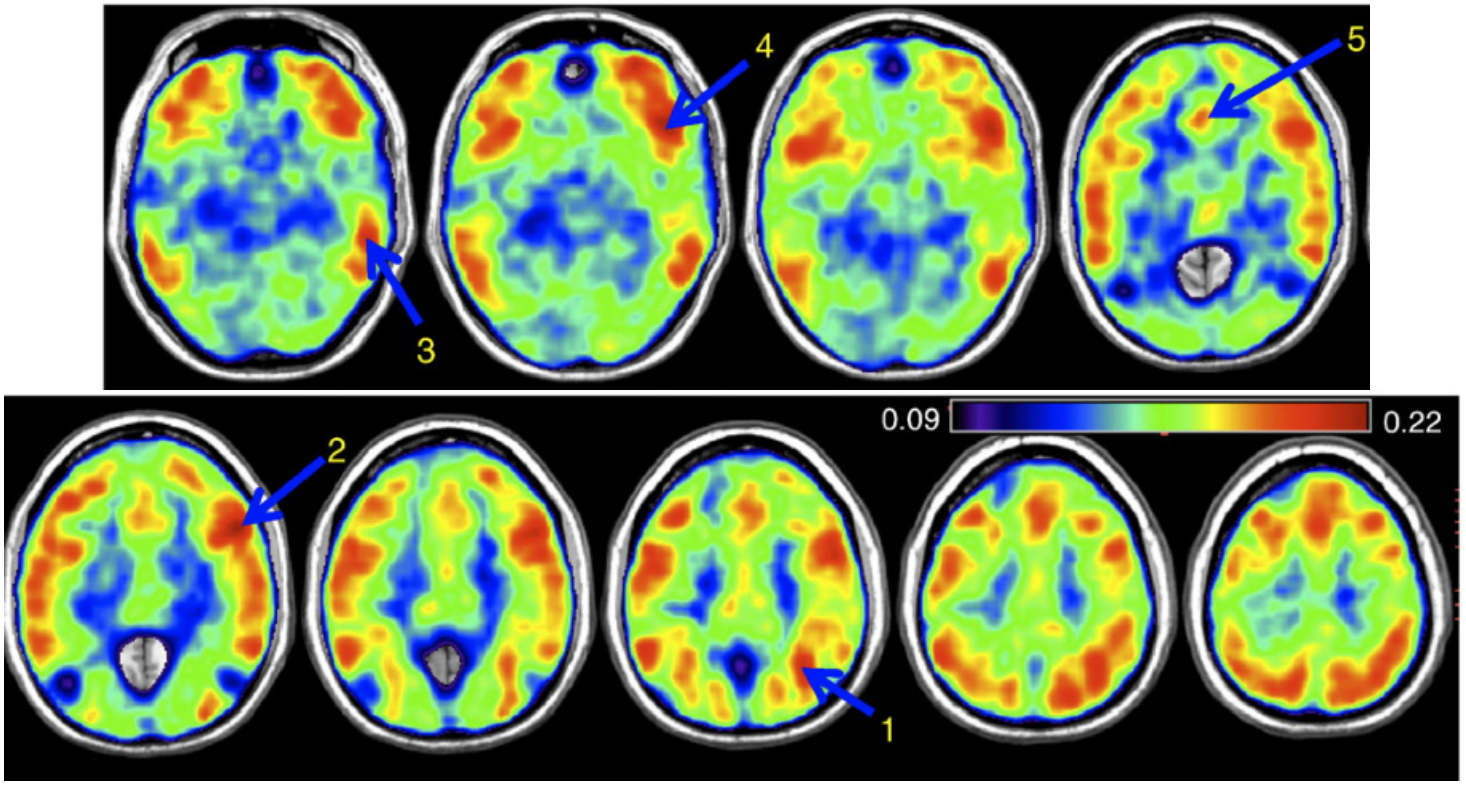
"Most studies of resting-state functional connectivity using fMRI employ methods that assume temporal stationarity, such as correlation and data-driven decompositions computed across the duration of the scan. However, evidence from task-based fMRI studies and animal electrophysiology suggests that functional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



Chang & Glover, NeuroImage 2009

Original Observations (I):Dynamic behavior varies across regions

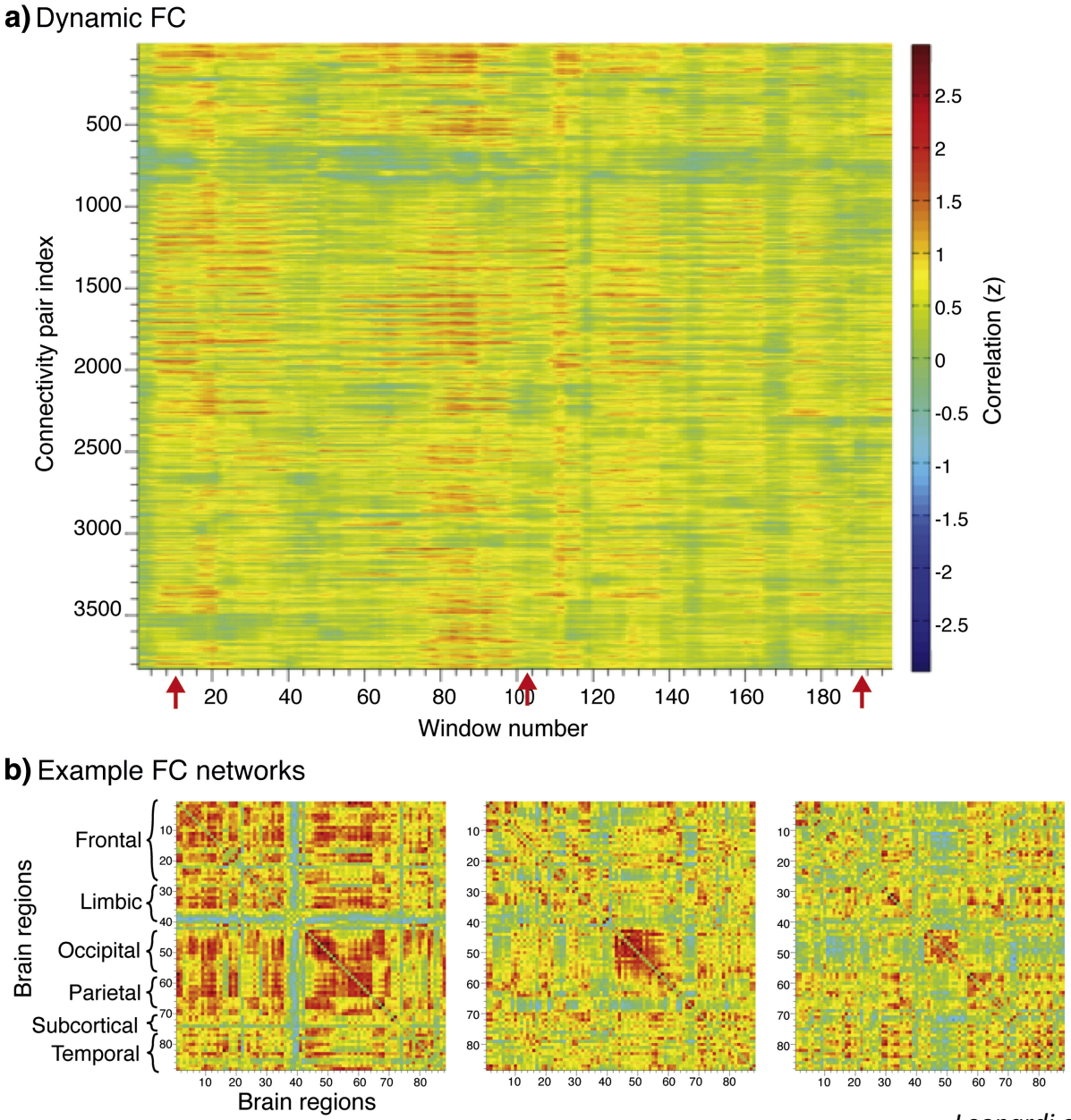
"Most studies of resting-state functional connectivity using fMRI employ methods that assume temporal stationarity, such as correlation and data-driven decompositions computed across the duration of the scan. However, evidence from task-based fMRI studies and animal electrophysiology suggests that functional 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."

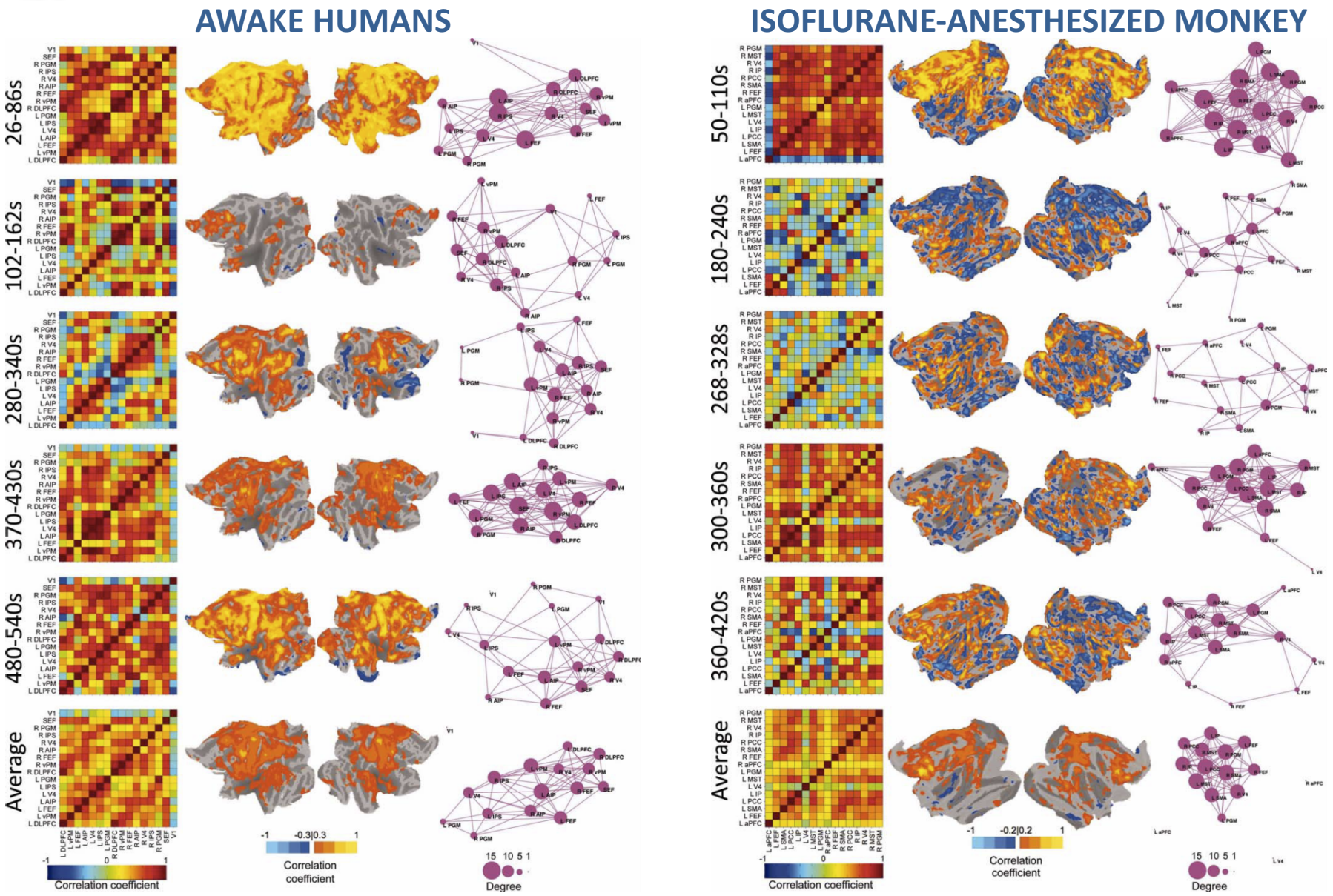
Chang & Glover, NeuroImage 2009

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



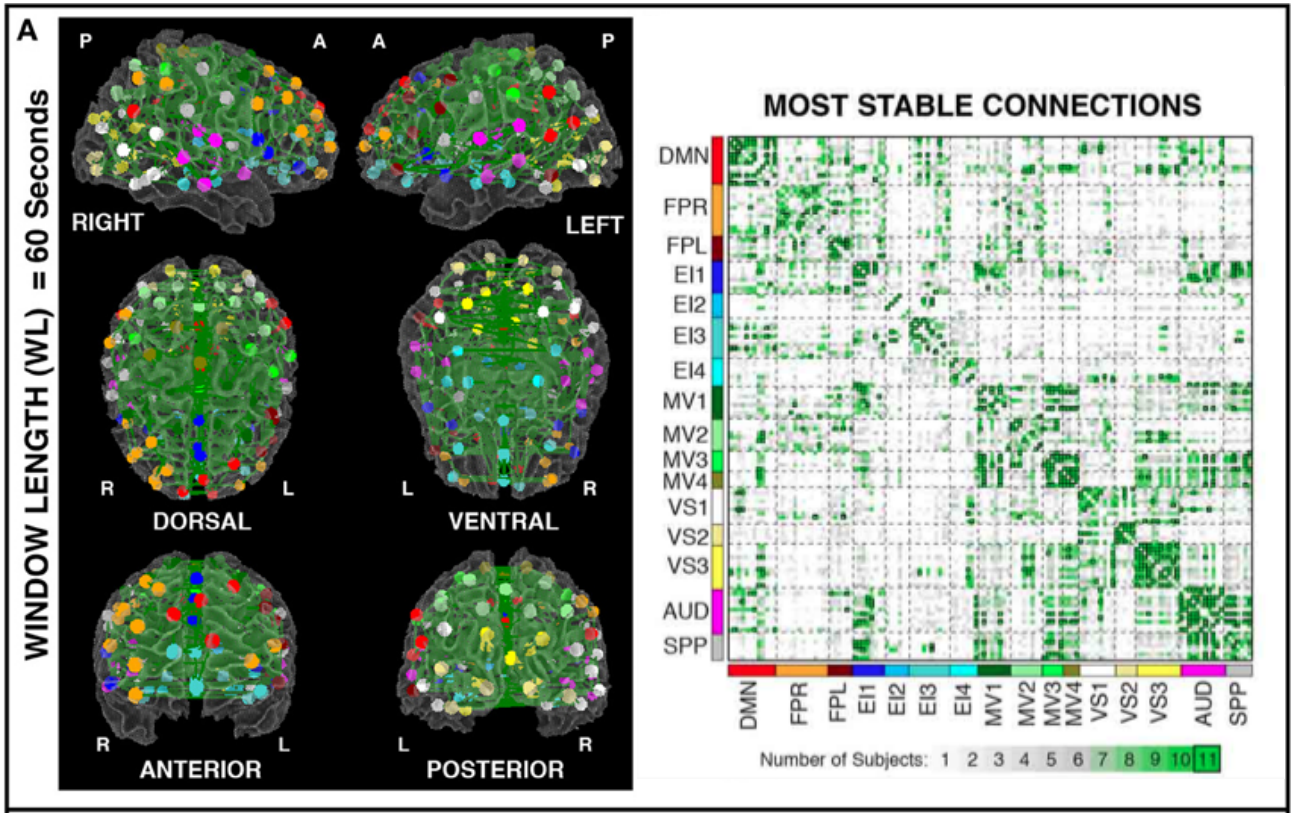
Leonardi et al. NeuroImage 2013

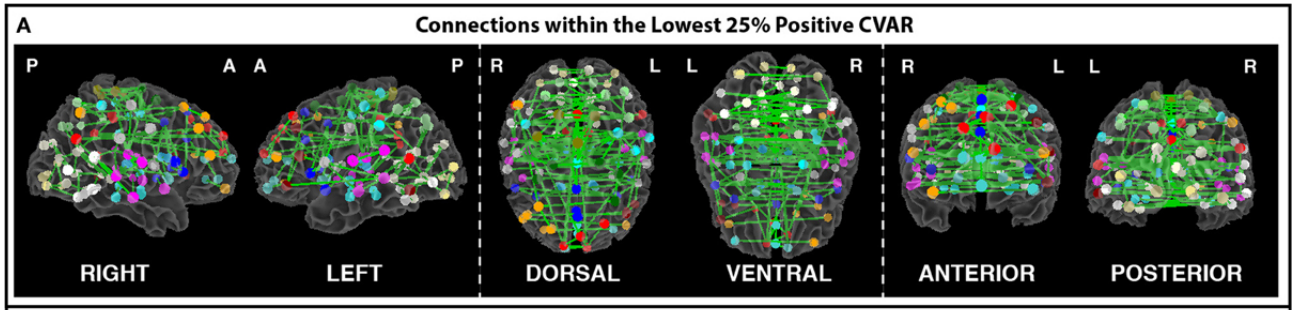
Original Observations (III): Dynamic FC also present in anaesthetized monkeys



Hutchison et al., Hum Brain Mapping 2013

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





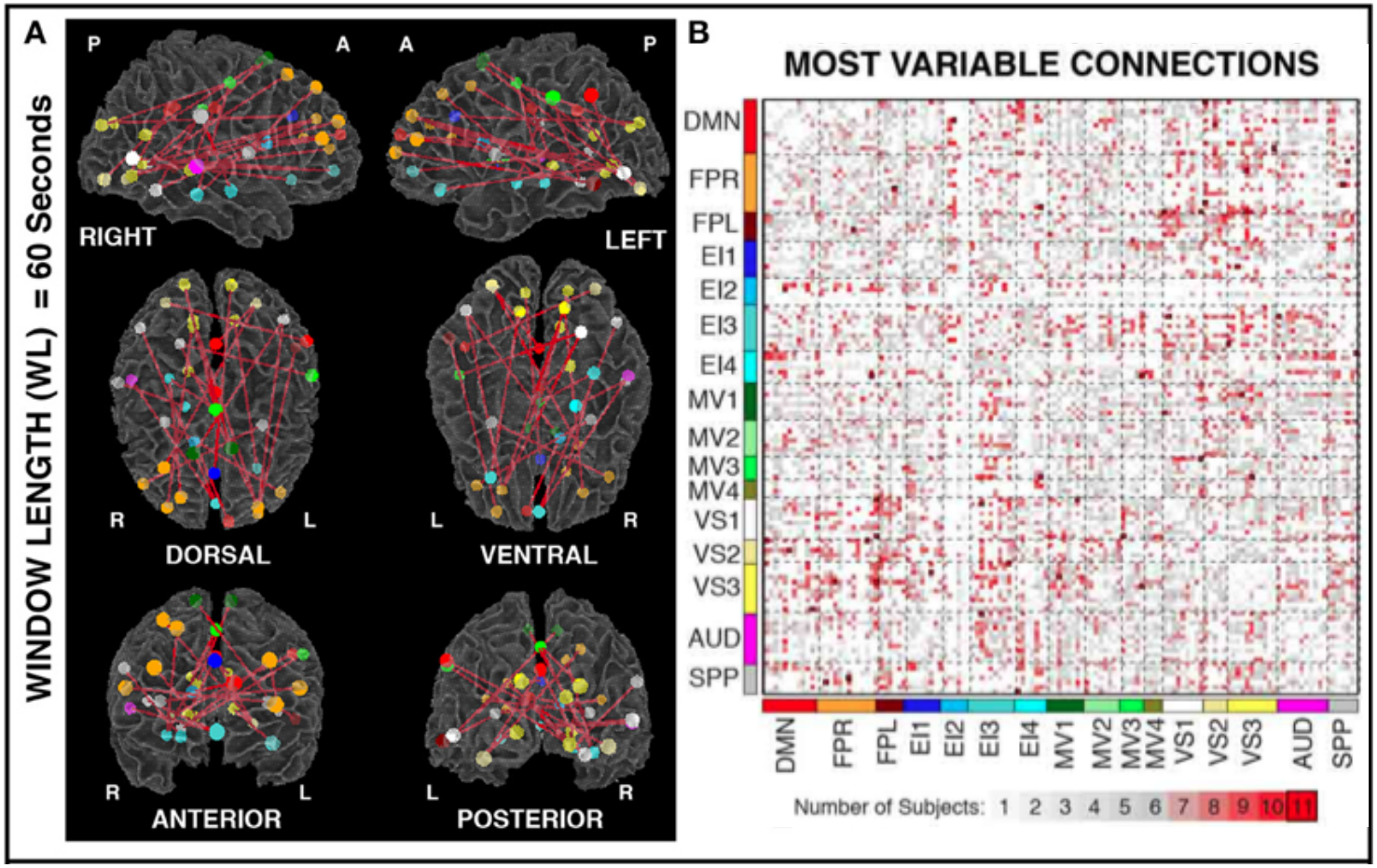
Mostly symmetric, inter-hemispheric connections between homologous right/left regions.

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

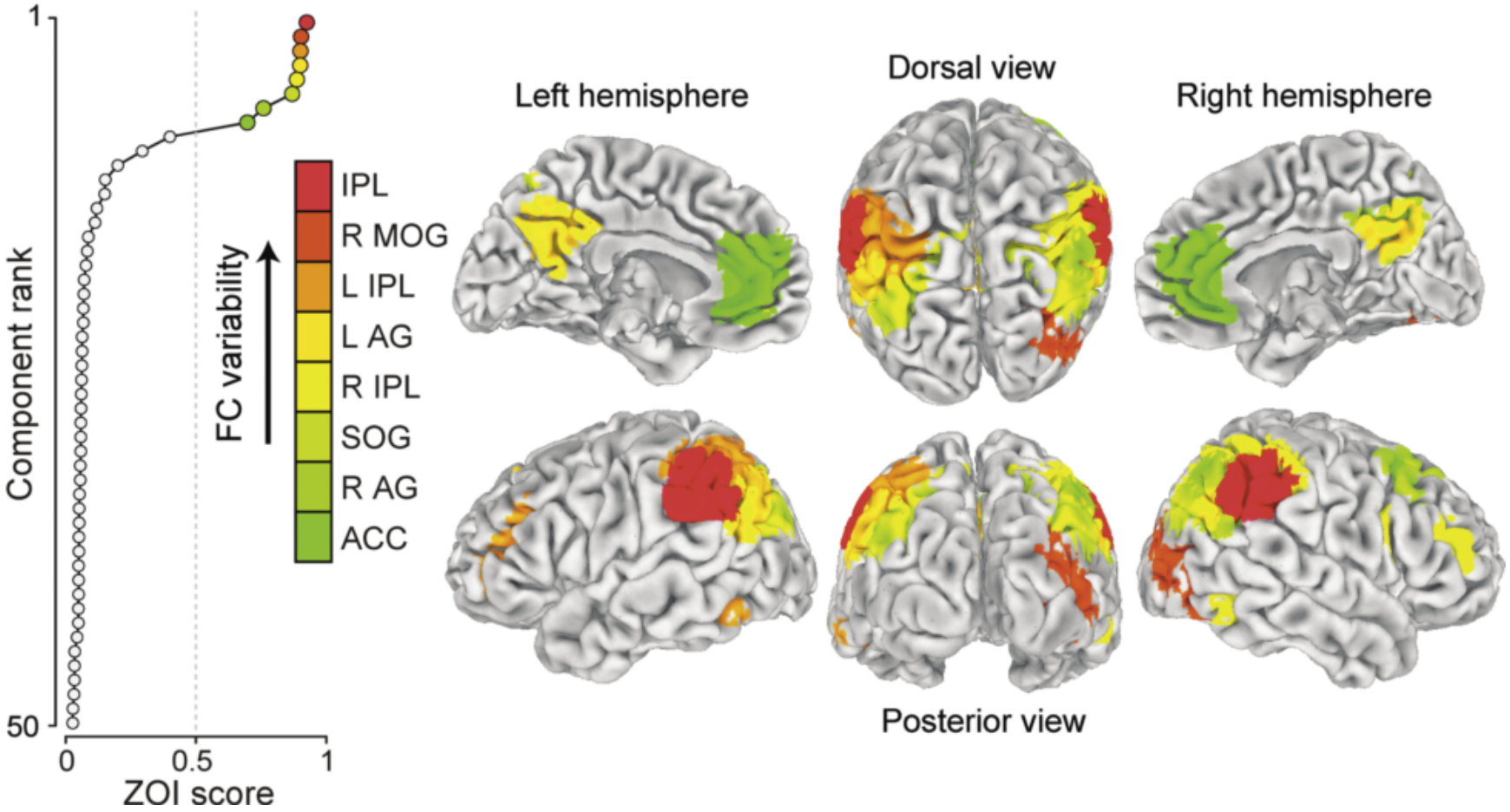
Spatial Distribution of Short Term FC Stability (I) – Most Variable Connections



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

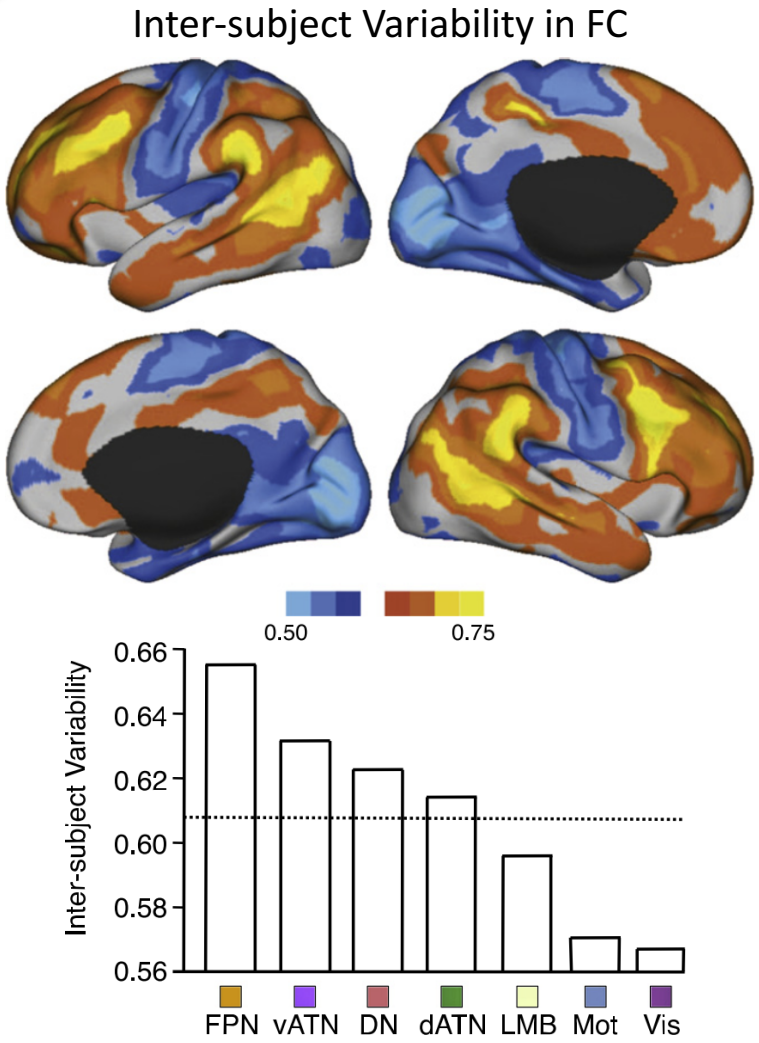
Spatial Distribution of Short Term FC Stability (II)

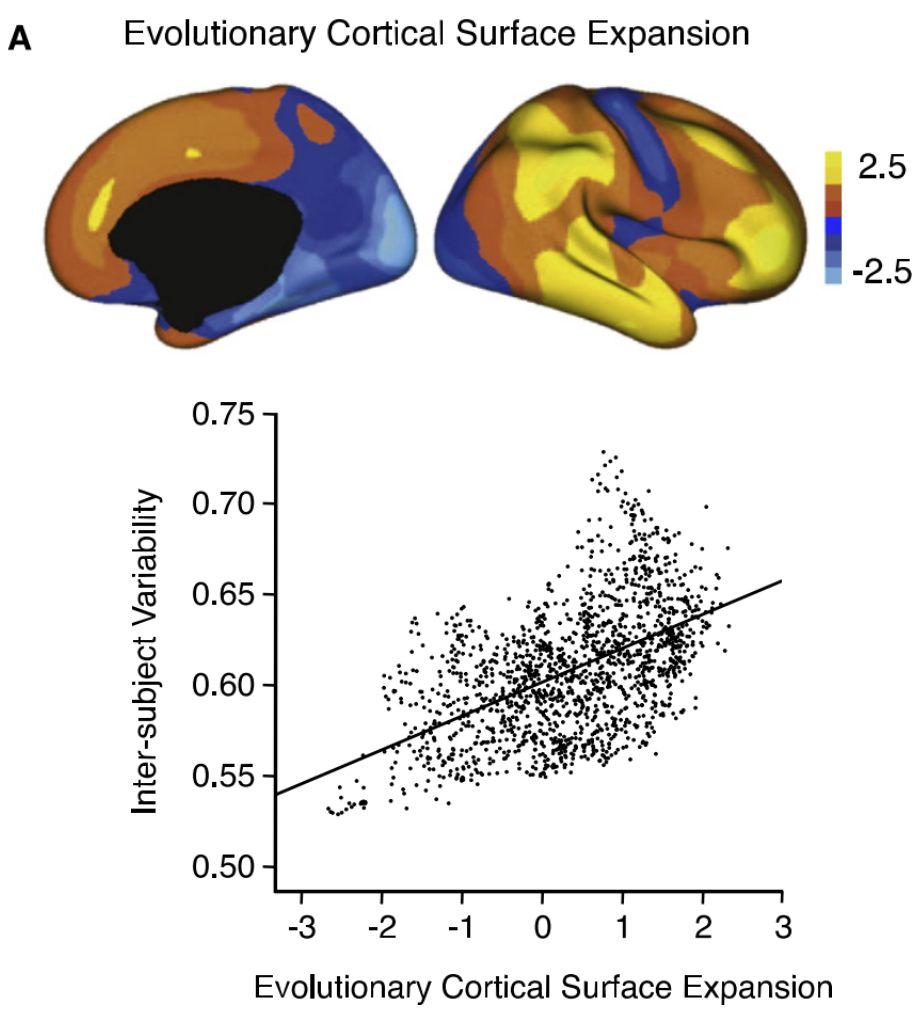


ZONE OF INSTABILITY: Set of Intrinsic Connectivity Networks with the most variable FC based on approx. 6 min long rest scans acquired on a group of 405 young adults and using a window length of 44 seconds.

Allen et al. Cerebral Cortex 2014

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





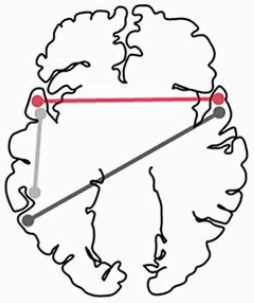
Higher inter-subject variability in FC in heteromodal association cortex and lower variability in unimodal cortex.

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)

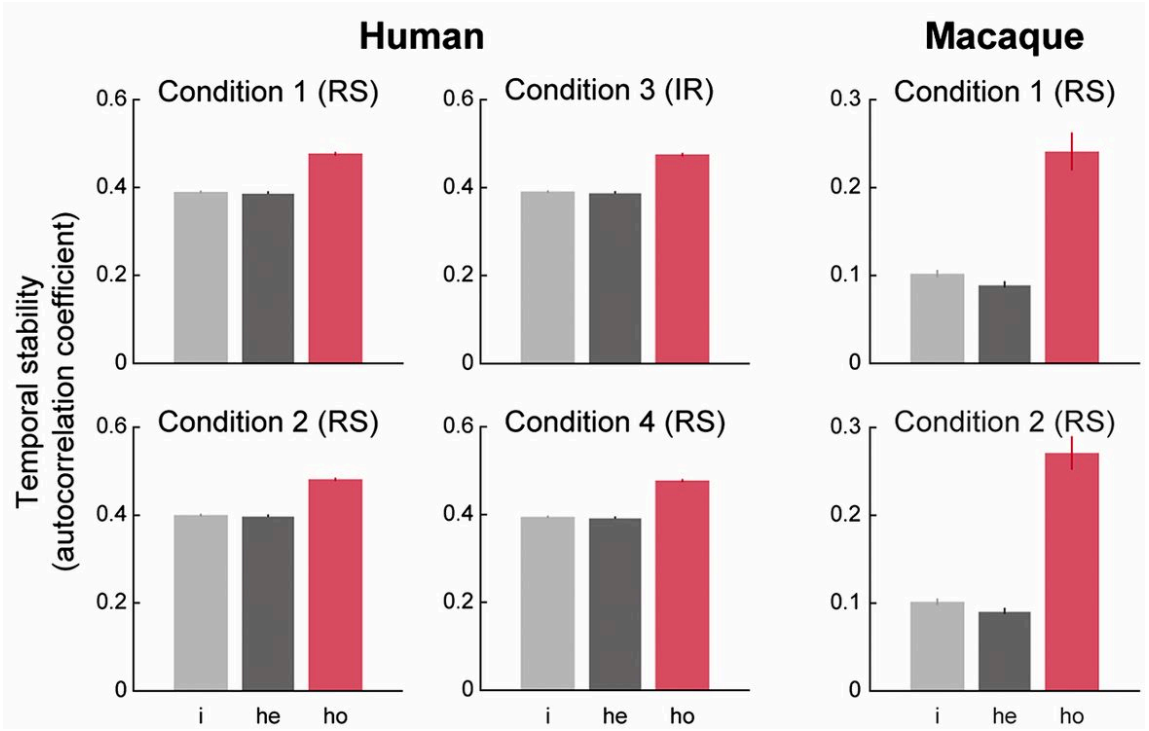


Connection type:
intrahemispheric (i)
heterotopic (he)
homotopic (ho)

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

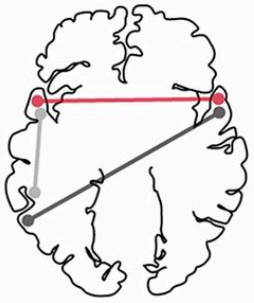
Across conditions & species, Homotopic FC is the most stable of all 3 types of connections.



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

Shen et al. PNAS 2015

FC Dynamics & Anatomical Connectivity (II)



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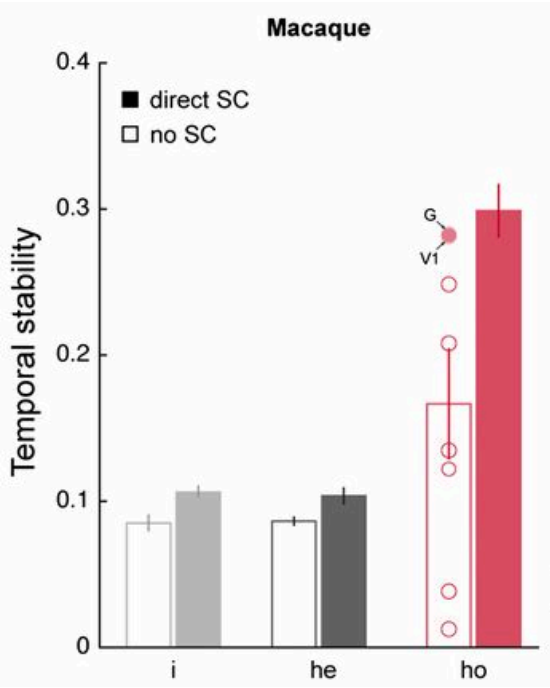
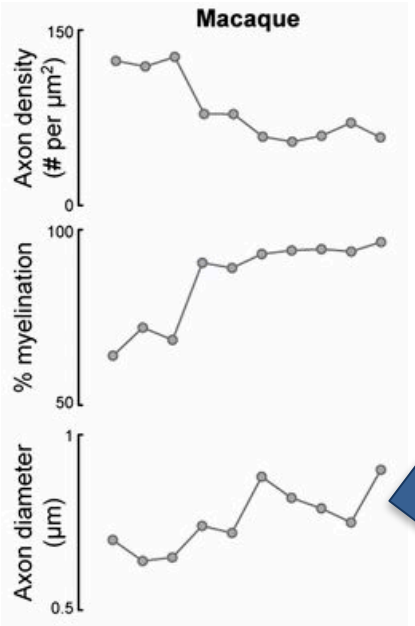
Macaque Data: 1 Condition Light Anesthesia

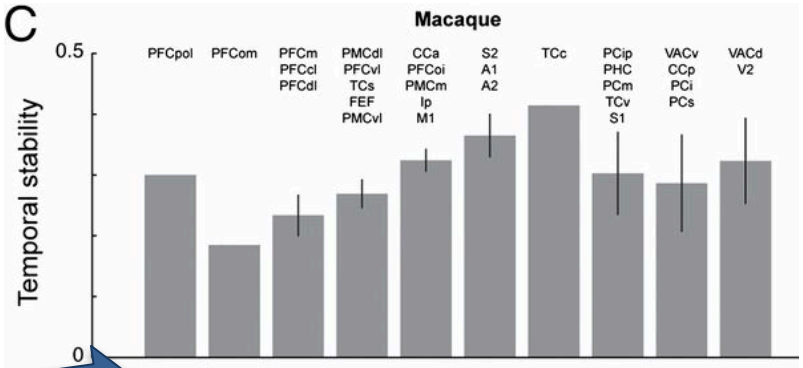
Temporal stability of homotopic FC is facilitated by direct anatomical projections and their conduction characteristics





Anterior ←→Posterior

Profile of temporal stability for homotopic connections with direct structural connectivity

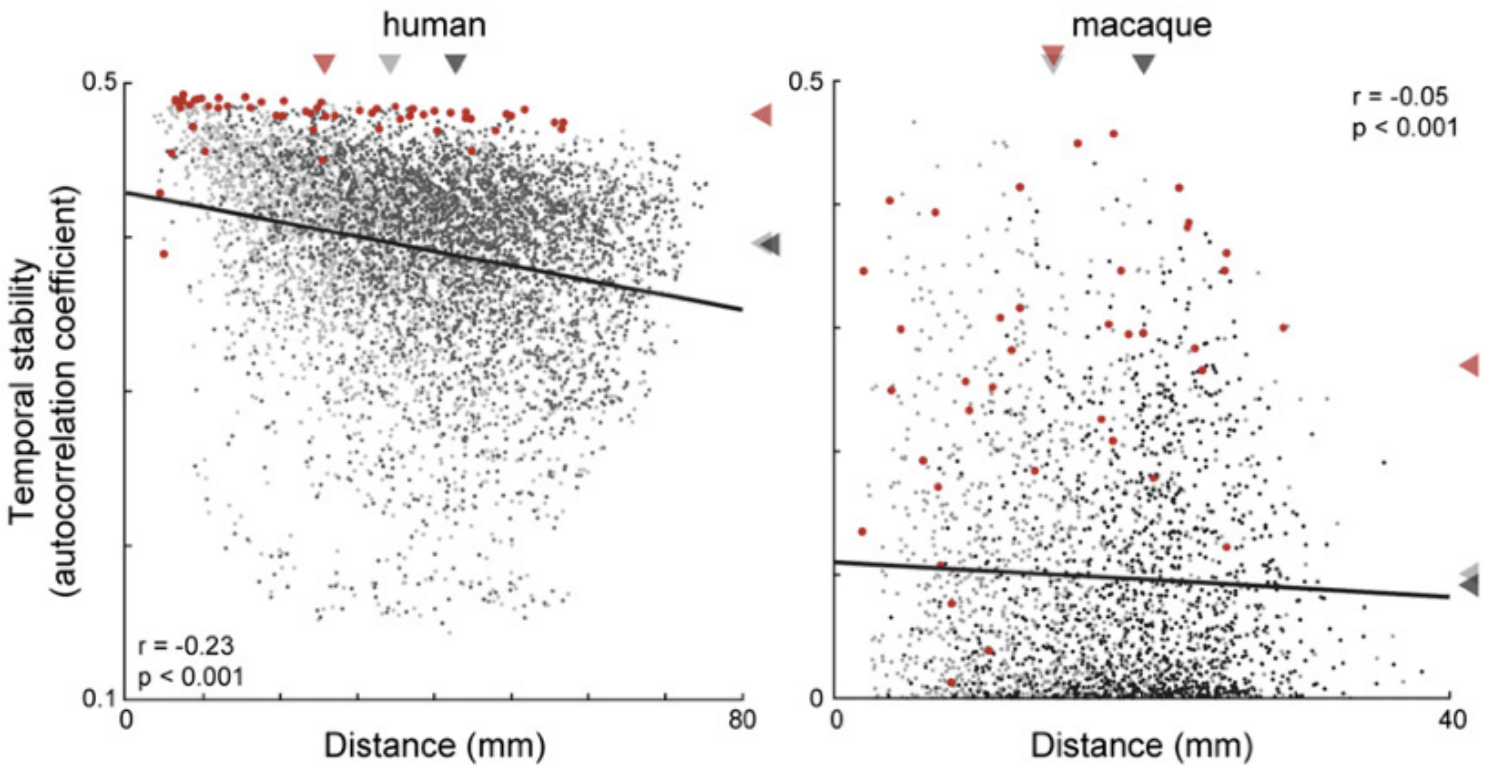


Anterior ←→Posterior

Shen et al. PNAS 2015

FC Dynamics cannot be explained simply by distance

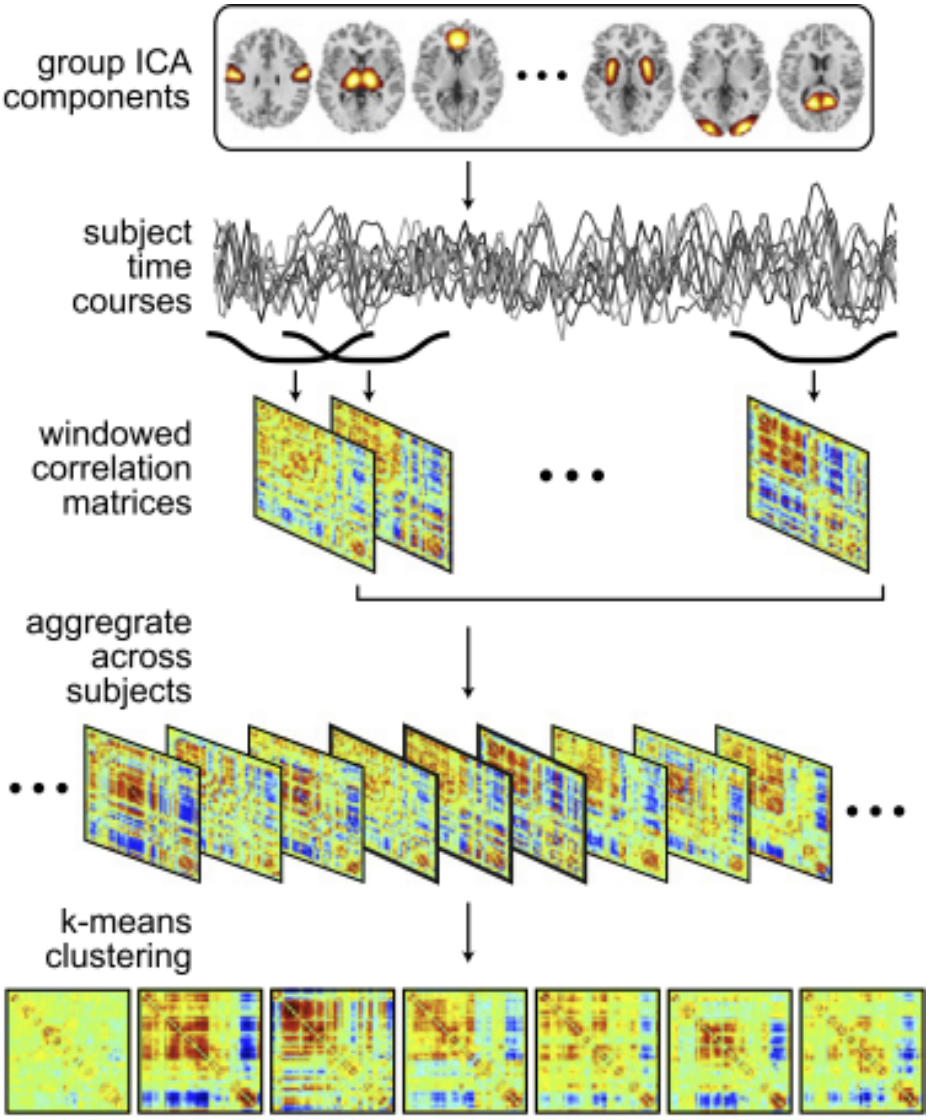
(5) FC Stability independent of distance



Shen et al. PNAS 2015

Reproducible Short-term patterns of FC – Connectivity States

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

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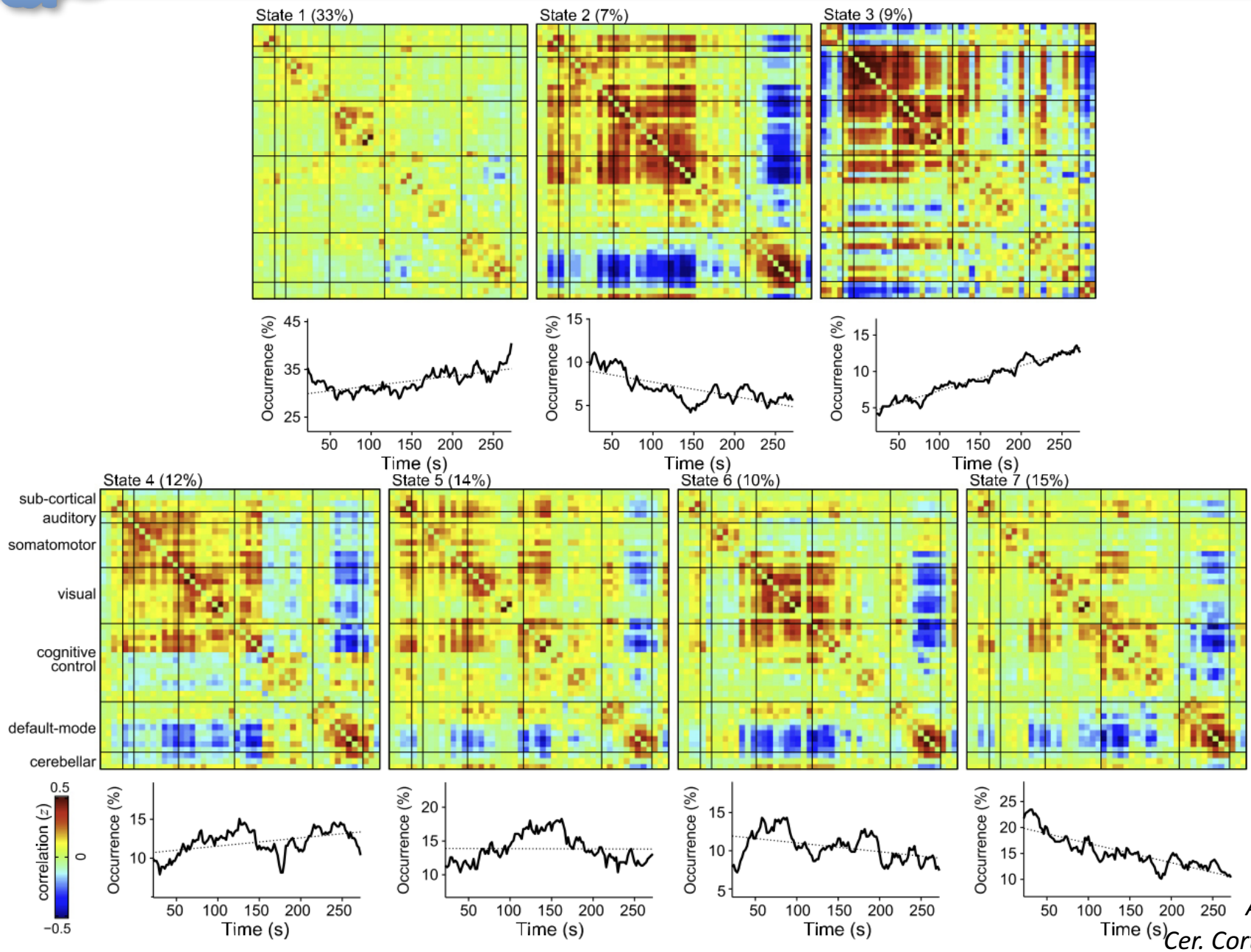

Allen et al. Cer. Cortex, 2014

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.**

Agenda

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  - Original observations
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- **RELATIONSHIP TO COGNITION / DISEASE**
  - Sleep Staging based on Dynamic FC Changes.
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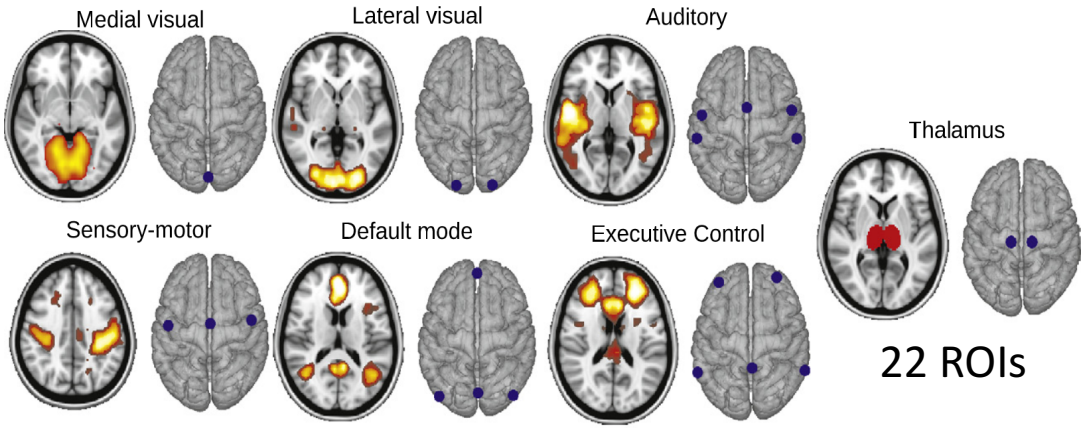
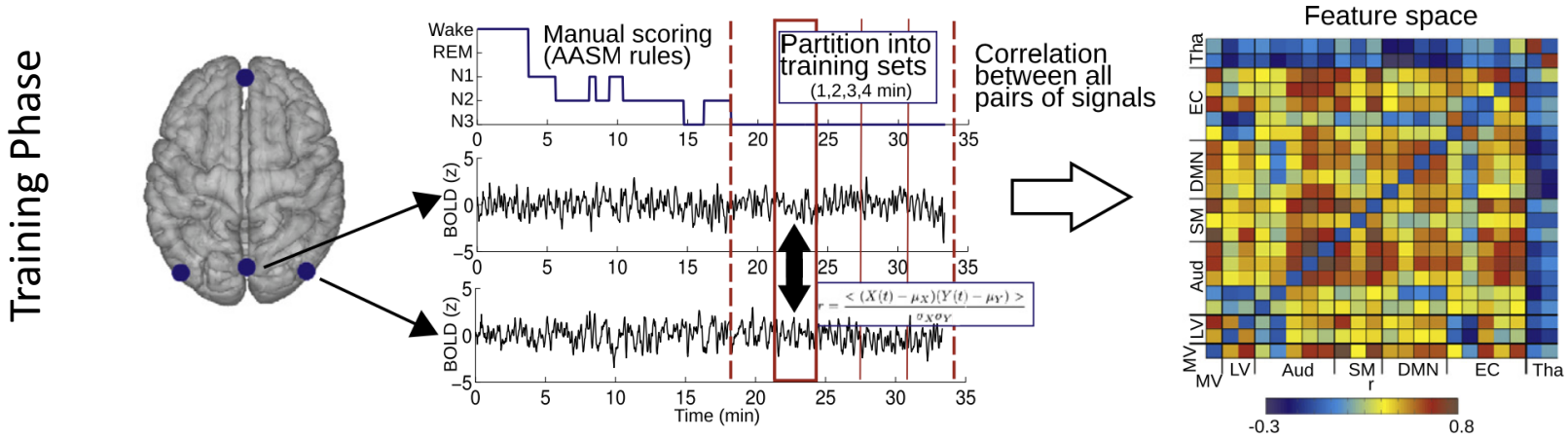
- **SOME COMMENTS ON METHODOLOGY**
  - Interpretational Issues with Sliding Window Correlation
  - Dynamic Conditional Correlation (DCC)
  - Dynamic Connectivity Detection (DCD)
  - Single-volume Co-Activation Patterns (CAPs)
  - Others…
- **CONCLUSIONS**

FC Dynamics vs. Sleep Stages

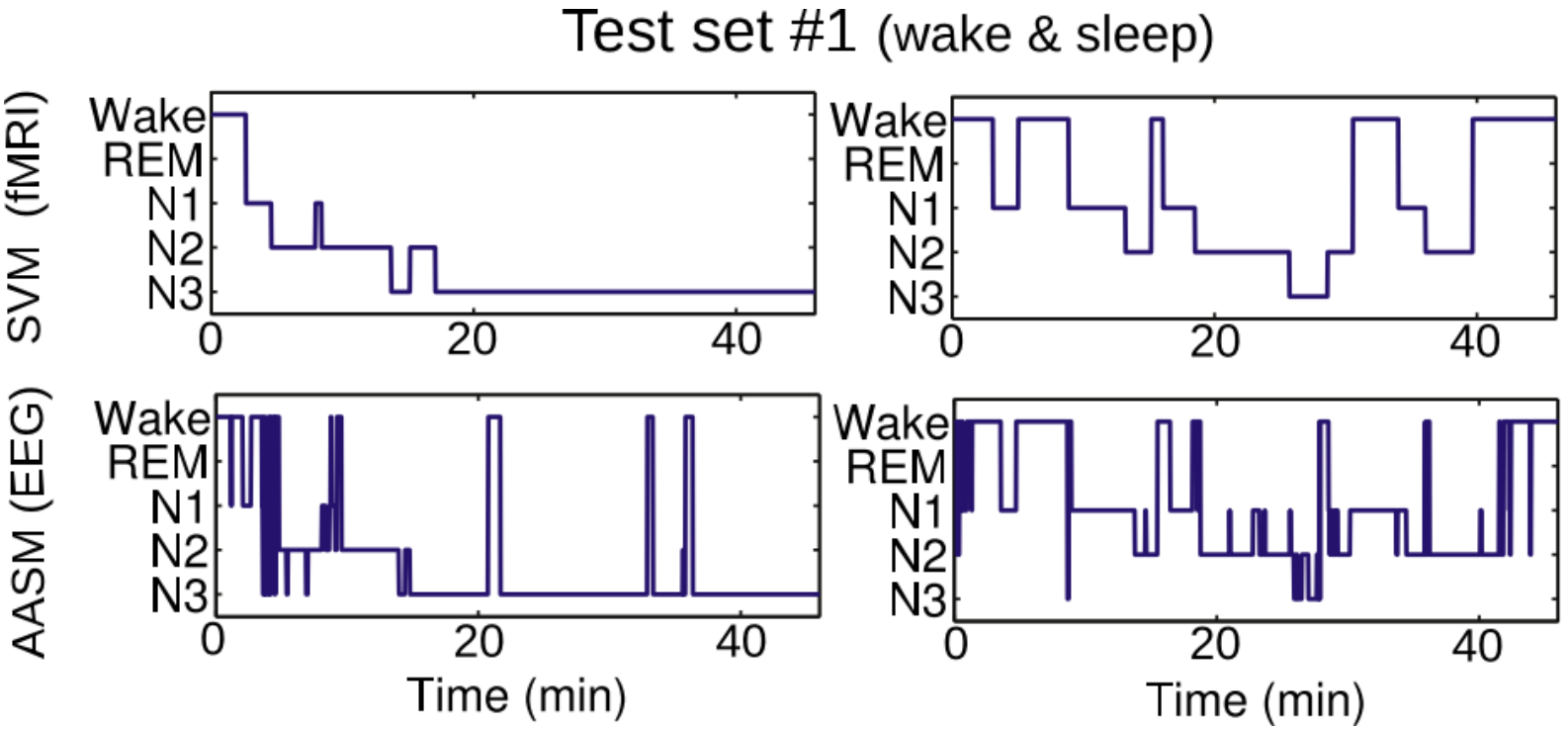
- Concurrent BOLD fMRI and EEG Recordings.
- Approx. 50 min long scans.
- Manual Sleep Staging based on EEG/AASM Criteria.
- WL = 60 s – 4 minutes





Algorithm: Multi-level Support Vector Machine

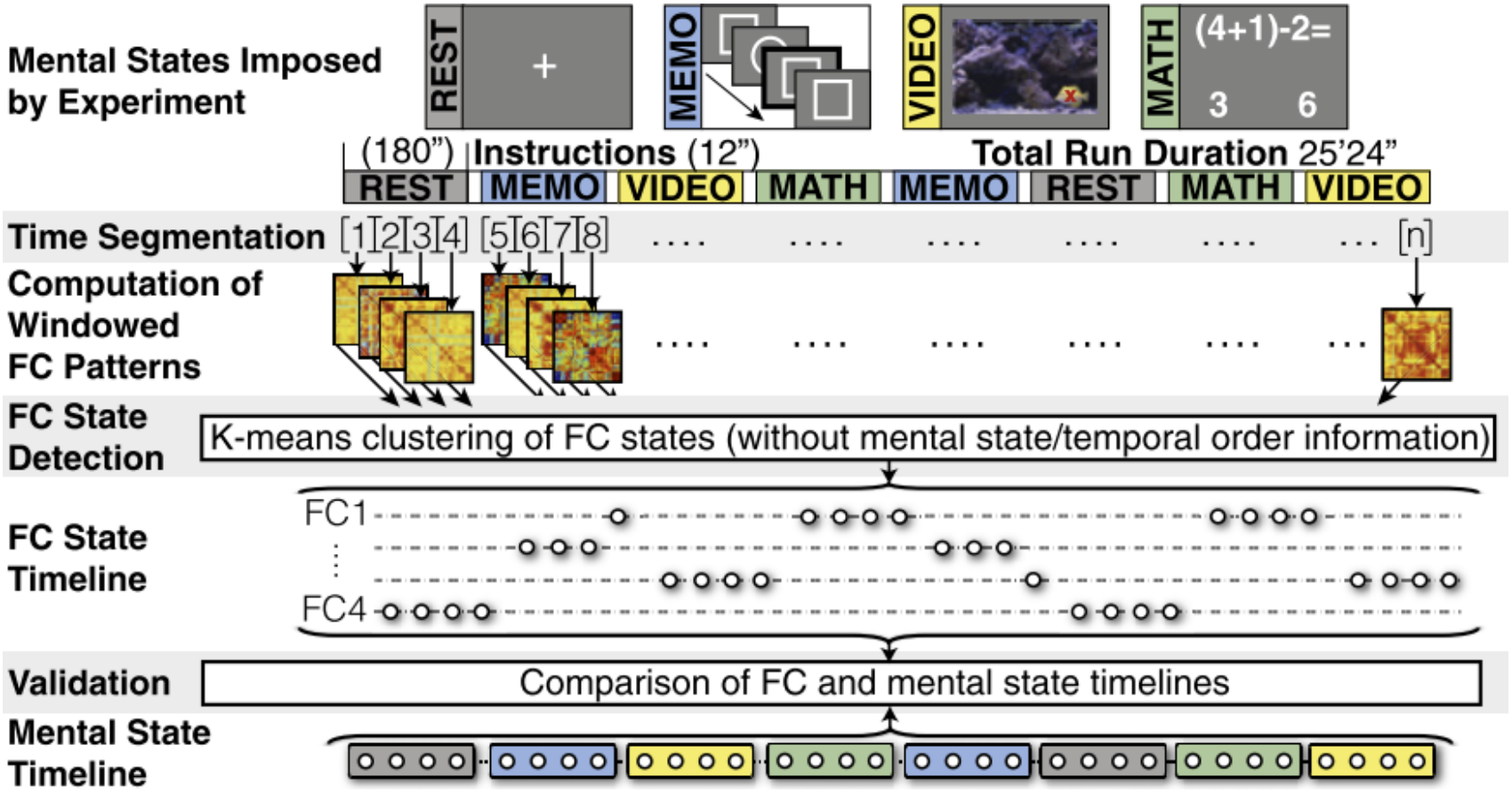
Tagliazucchi et al. NeuroImage 2012



80% Accuracy for WL = 2 mins and above

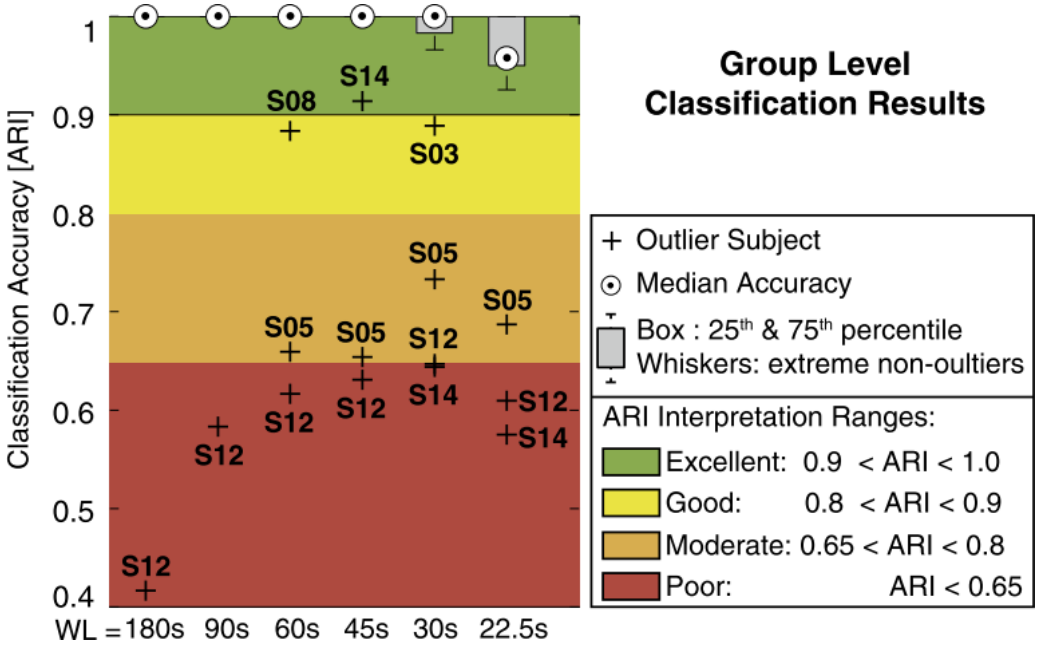
Tagliazucchi et al. NeuroImage 2012

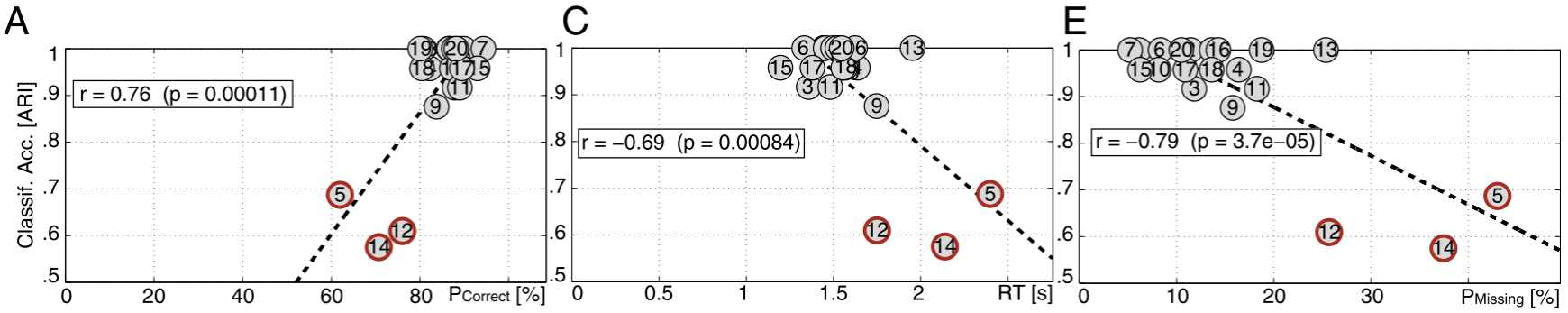
FC Dynamics vs. Mental States Imposed by Task (I)



Gonzalez-Castillo et al. PNAS 2015

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

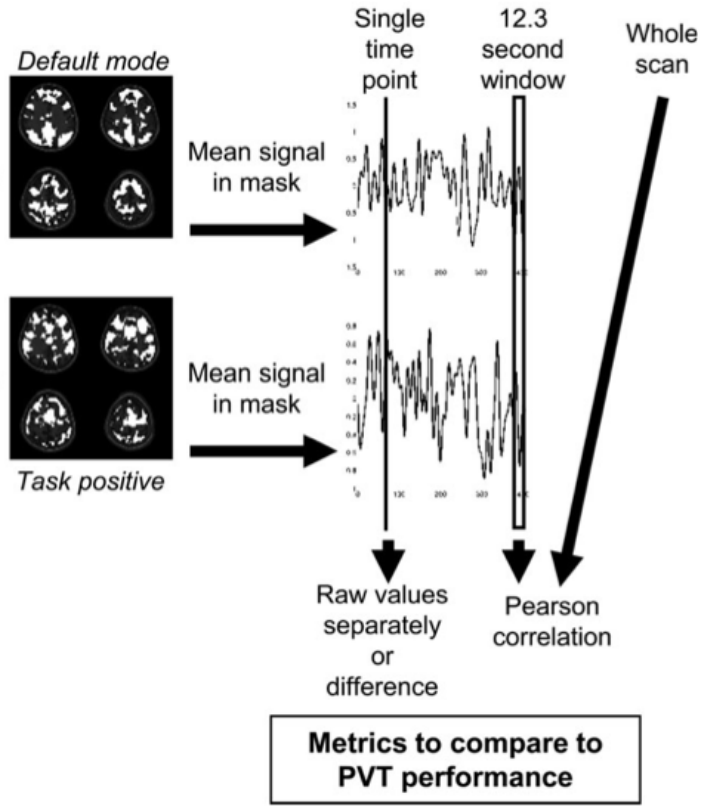




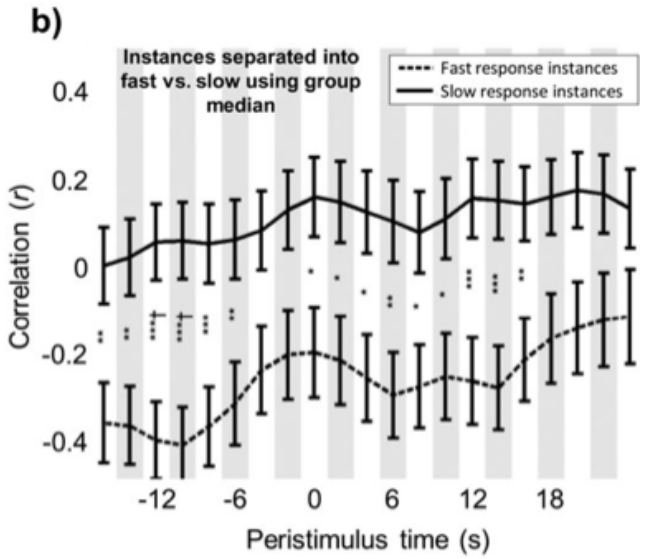
Gonzalez-Castillo et al. PNAS 2015

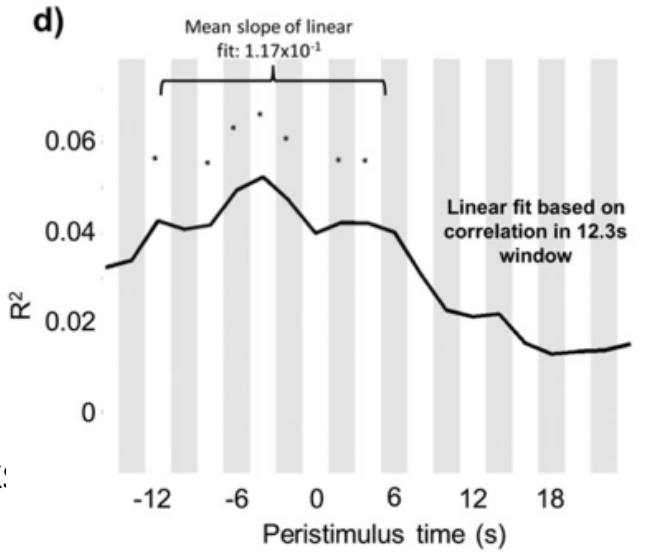
FC Dynamics vs. Task Outcome Prediction

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



TR = 300ms

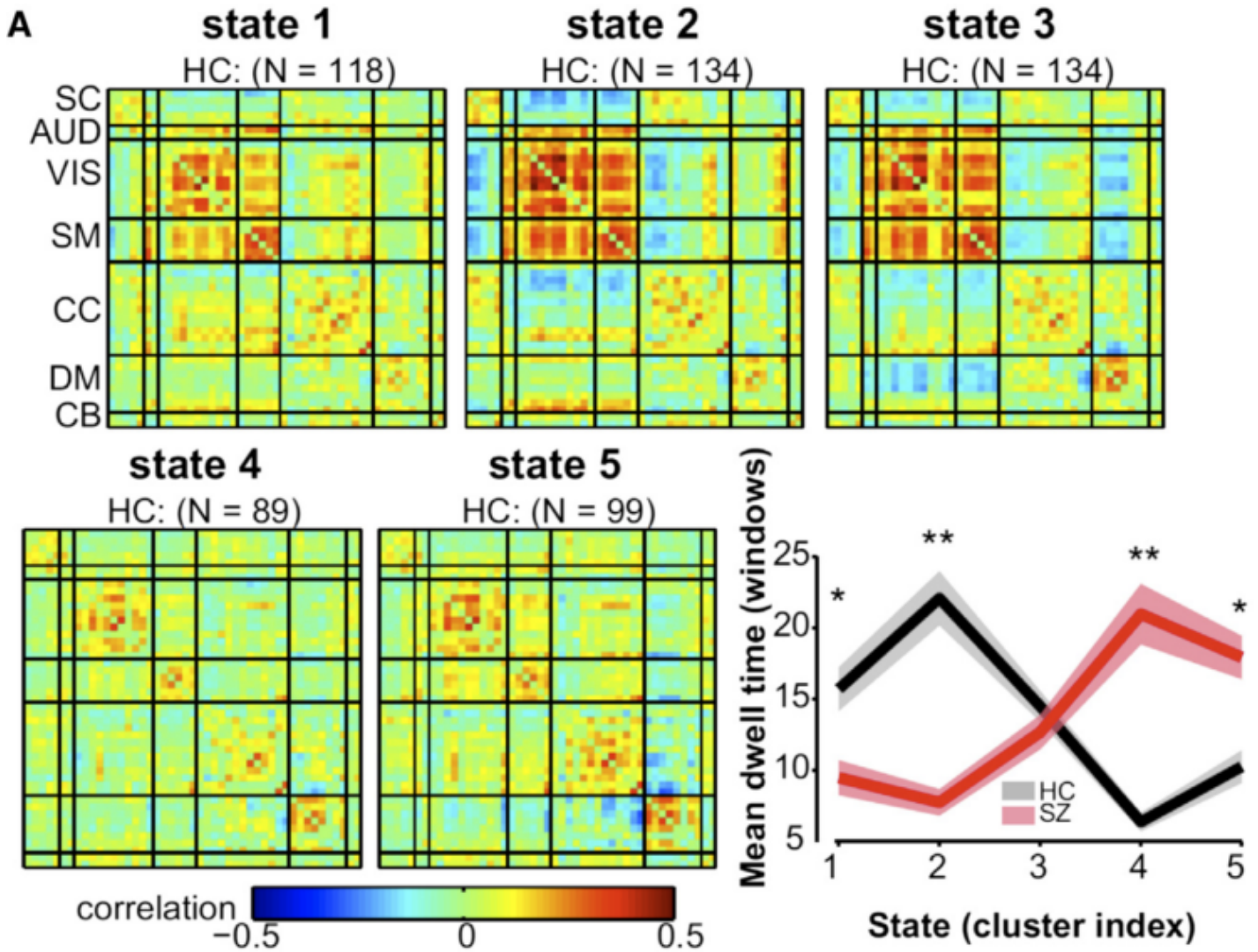




In most cases, more anti-correlation between network was significantly related to faster performance.

Thompson et al. Human Brain Mapping 2013

Alterations of Dynamic Connectivity & Disease (I): Schizophrenia

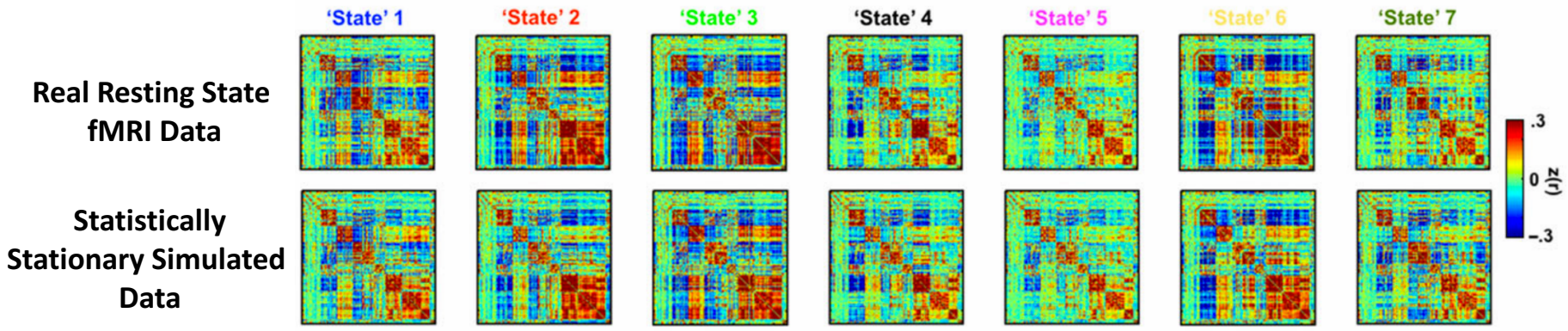


Dynamic states in a large (n > 300) data set of schizophrenia patients and controls in which the patients are spending significantly more time in the relatively less connected state 4.

Damaraju et al. NeuroImage Clinical, 2014

A word of caution…

"Here, using simulations and multiple sets of empirical observations, we ***confirm that imposed task states can alter the correlation structure of BOLD activity****. However, we find that* ***observations of "dynamic" BOLD correlations during the resting state are largely explained by sampling variability****. Beyond sampling variability, the largest part of observed "dynamics" during rest is attributable to* ***head motion****. An additional component of dynamic variability during rest is attributable to* ***fluctuating sleep state****. Thus, aside from the preceding explanatory factors,* ***a single correlation structure—as opposed to a sequence of distinct correlation structures—may adequately describe the resting state as measured by BOLD fMRI."***



Stationary Process: "one whose spectral content and moments (e.g., mean, variance, etc.) are constant over time... stationarity does not mean a still process."

Laumann et al., Cerebral Cortex (2016)

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…

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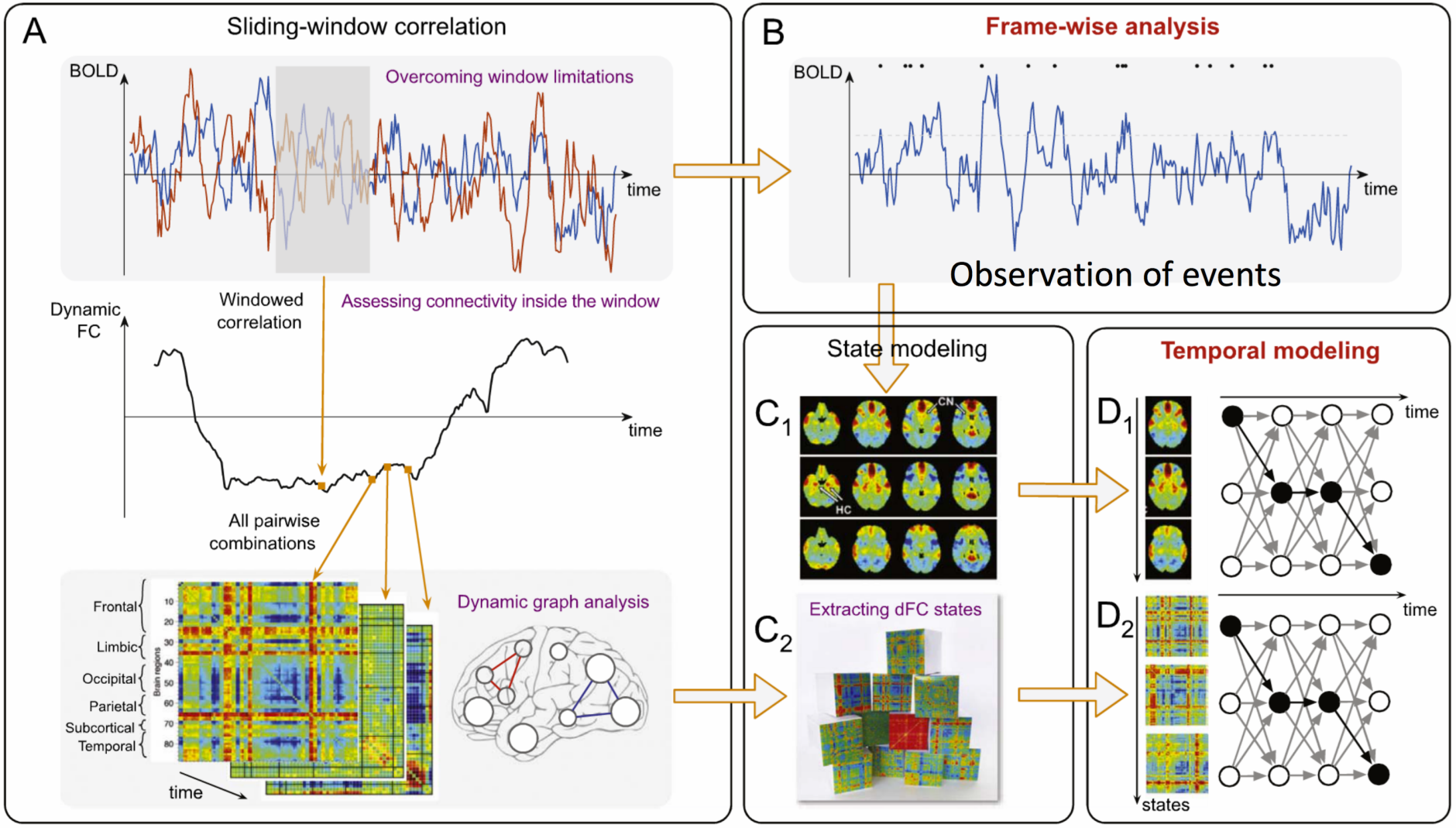
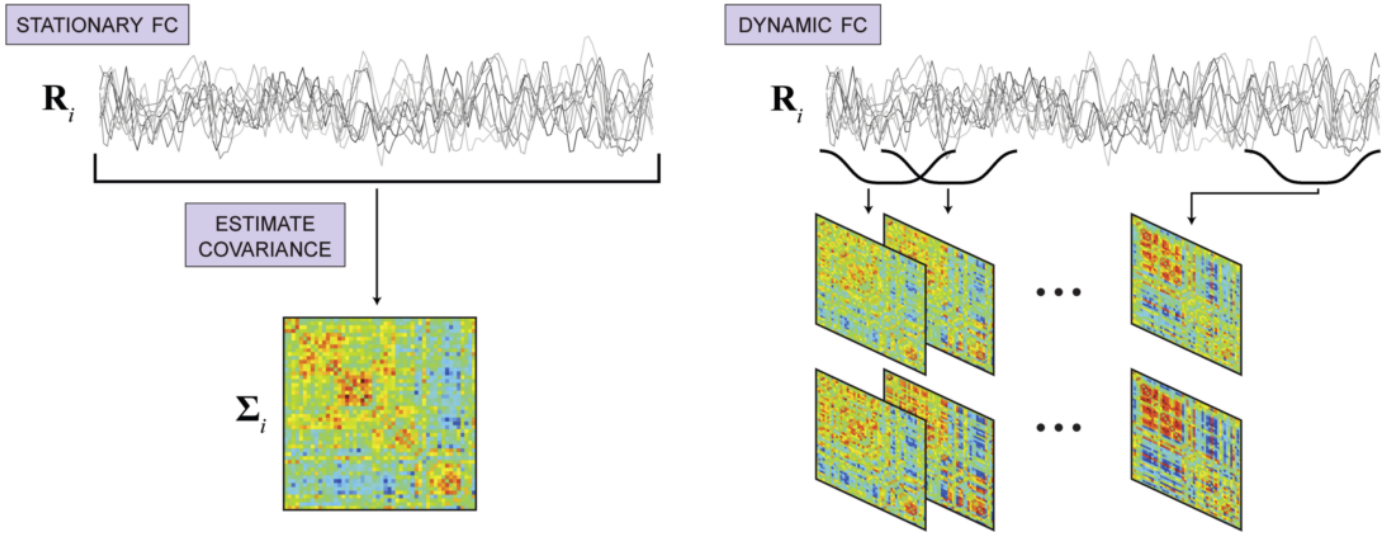
Two Main Approaches



Preti et al. NeuroImage 2016

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.

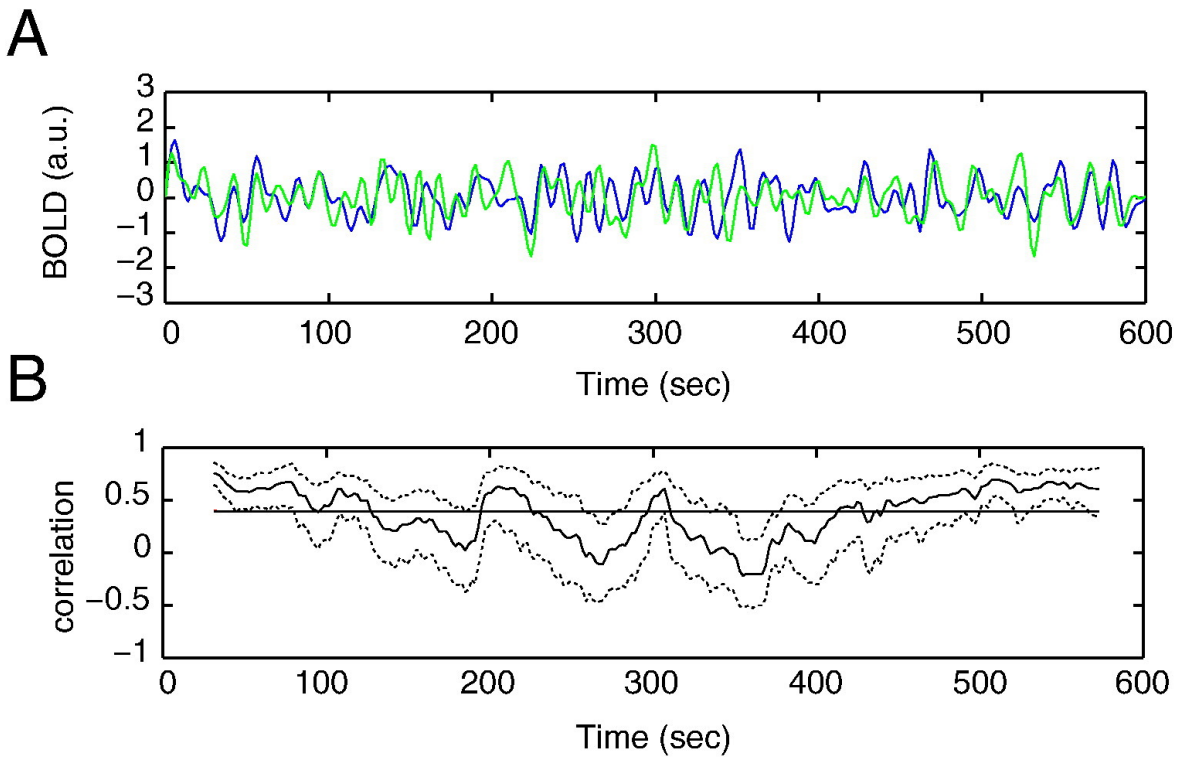
CONS:

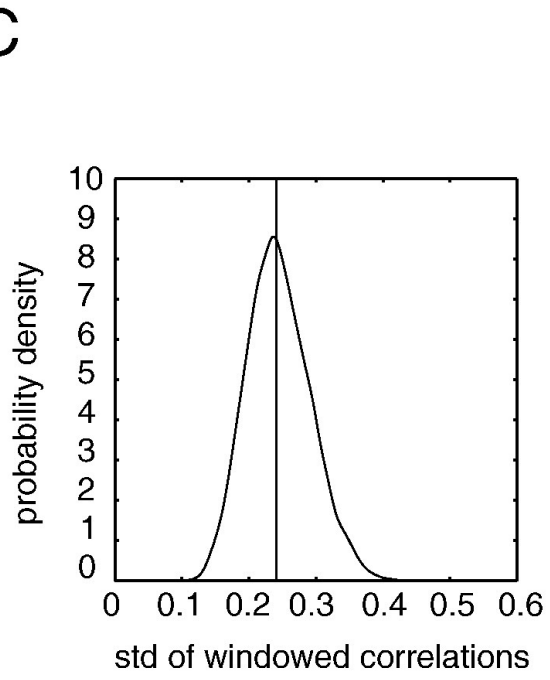
- Requires a-priori selection of WL
- Too short WL → may render connectivity estimates unreliable
- Too long WL → may impede observation of phenomena of interest
- Interpretation is more complex that it seems.
- WL limits the analysis to fluctuations in the freq. range below the window period, independently of the true frequency content of the data

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."

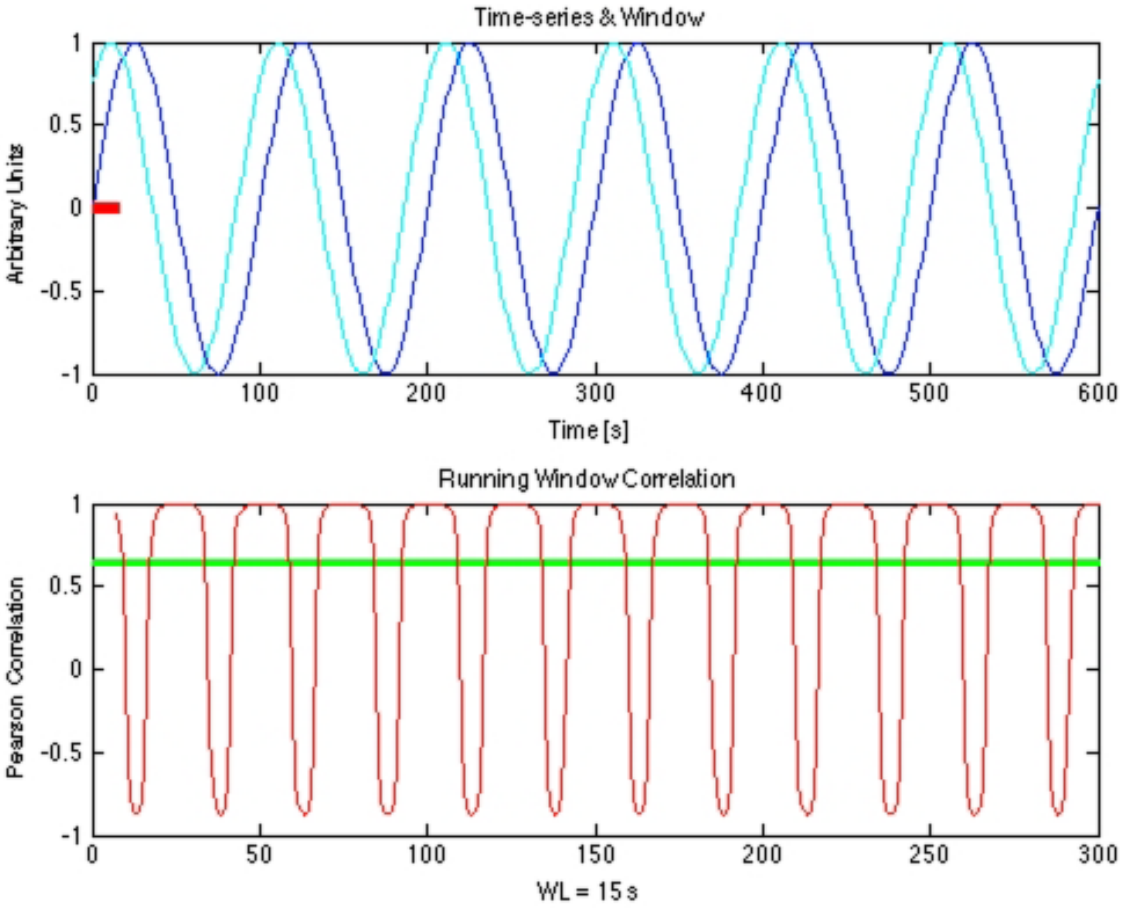




Hindriks et al. NeuroImage 2016

Sliding Window Correlation: Spurious Correlations (I)

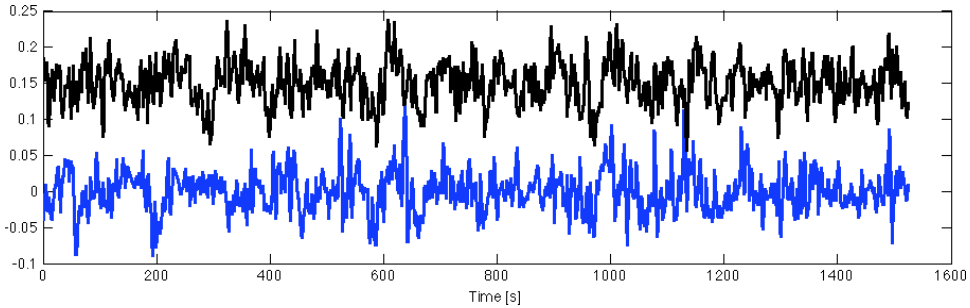
WL < 1 Period of slower fluctuation ➔ Spurious fluctuations in correlation traces will appear



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

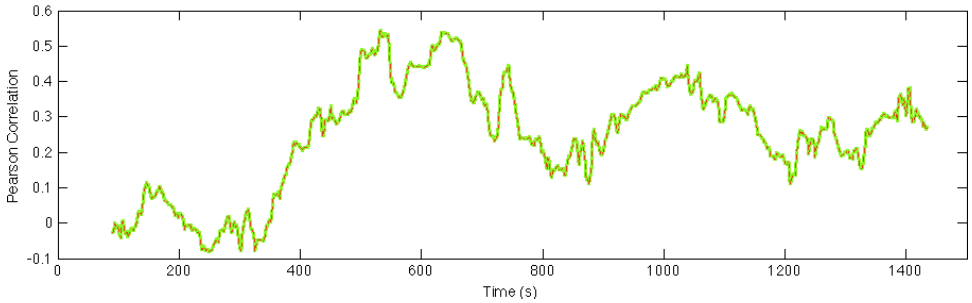
Sliding Window Correlation: Spurious Fluctuations (II)



Signal from 2 ROIs

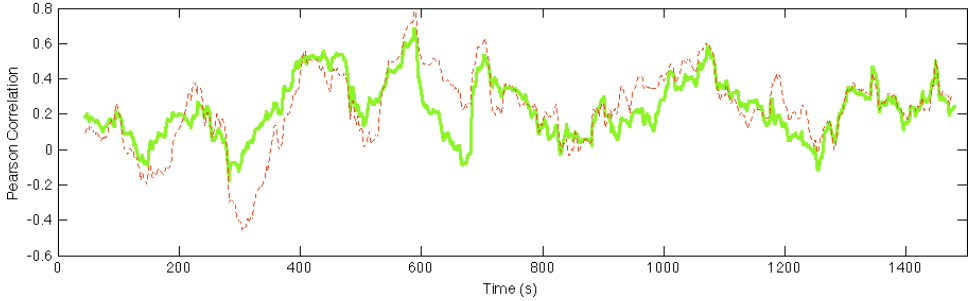
Time series of sliding window correlations between both ROIs

WL = 180s



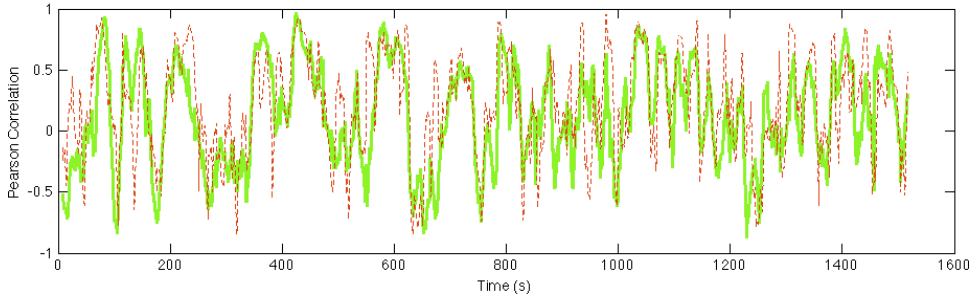
0.006 – 0.18Hz

WL = 90s



0.011 – 0.18Hz
0.006 – 0.18Hz

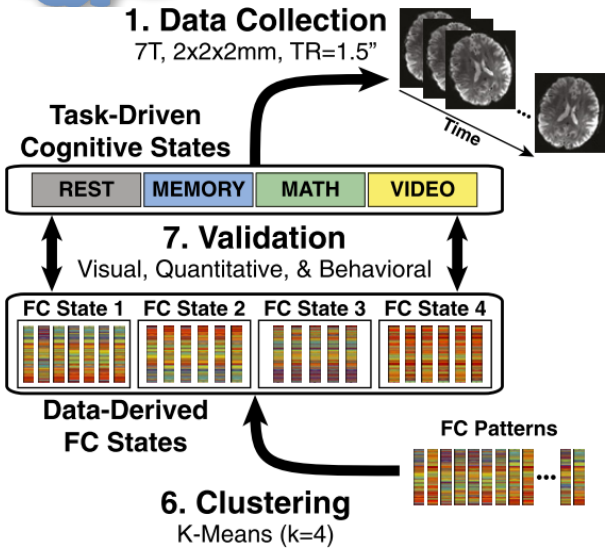
WL = 15s

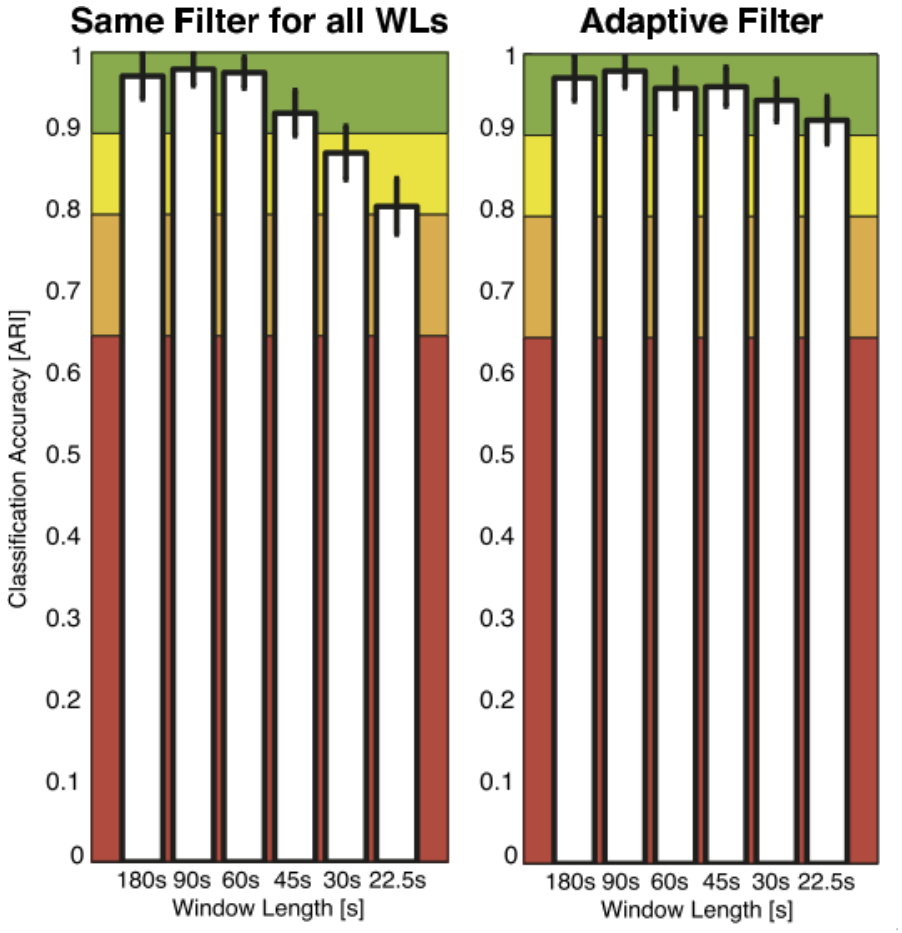


0.066 – 0.18Hz
0.006 – 0.18Hz

Leonardi et al. 2015

Sliding Window Correlation: Spurious Fluctuations (II)

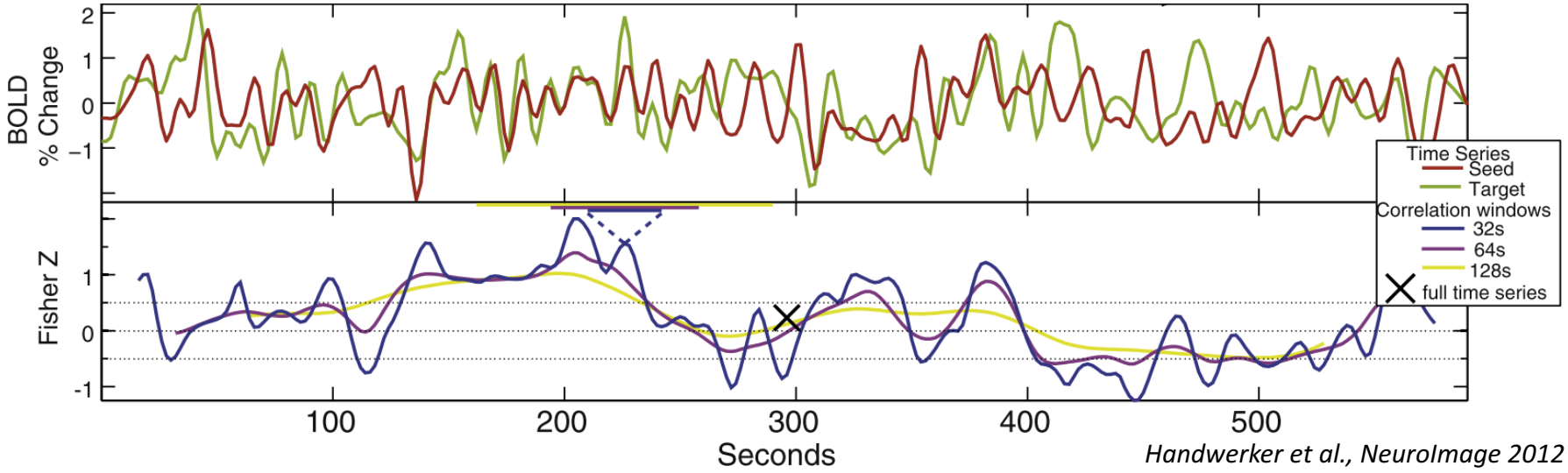




Gonzalez-Castillo et al., PNAS 2015

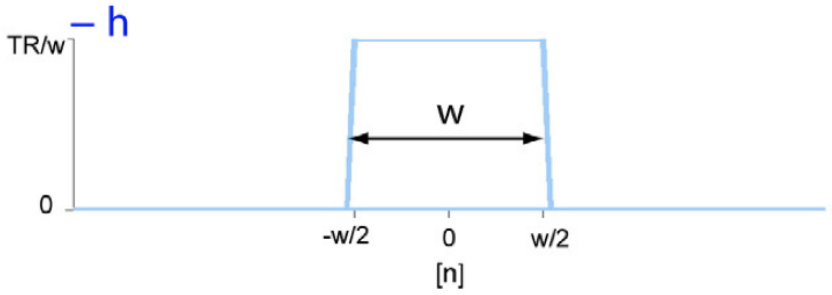
Sliding Window Correlation: Window Length vs. Amount of Fluctuation

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

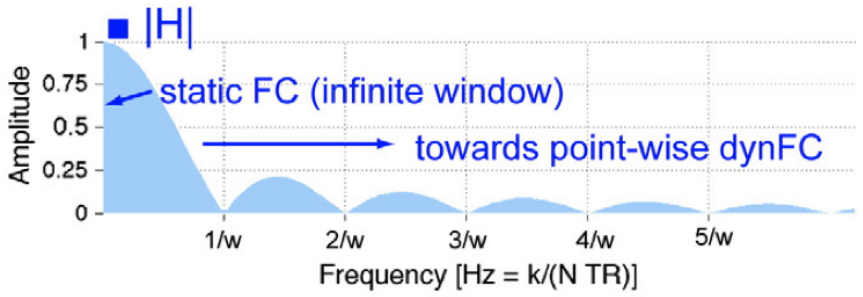


Handwerker et al., NeuroImage 2012

***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

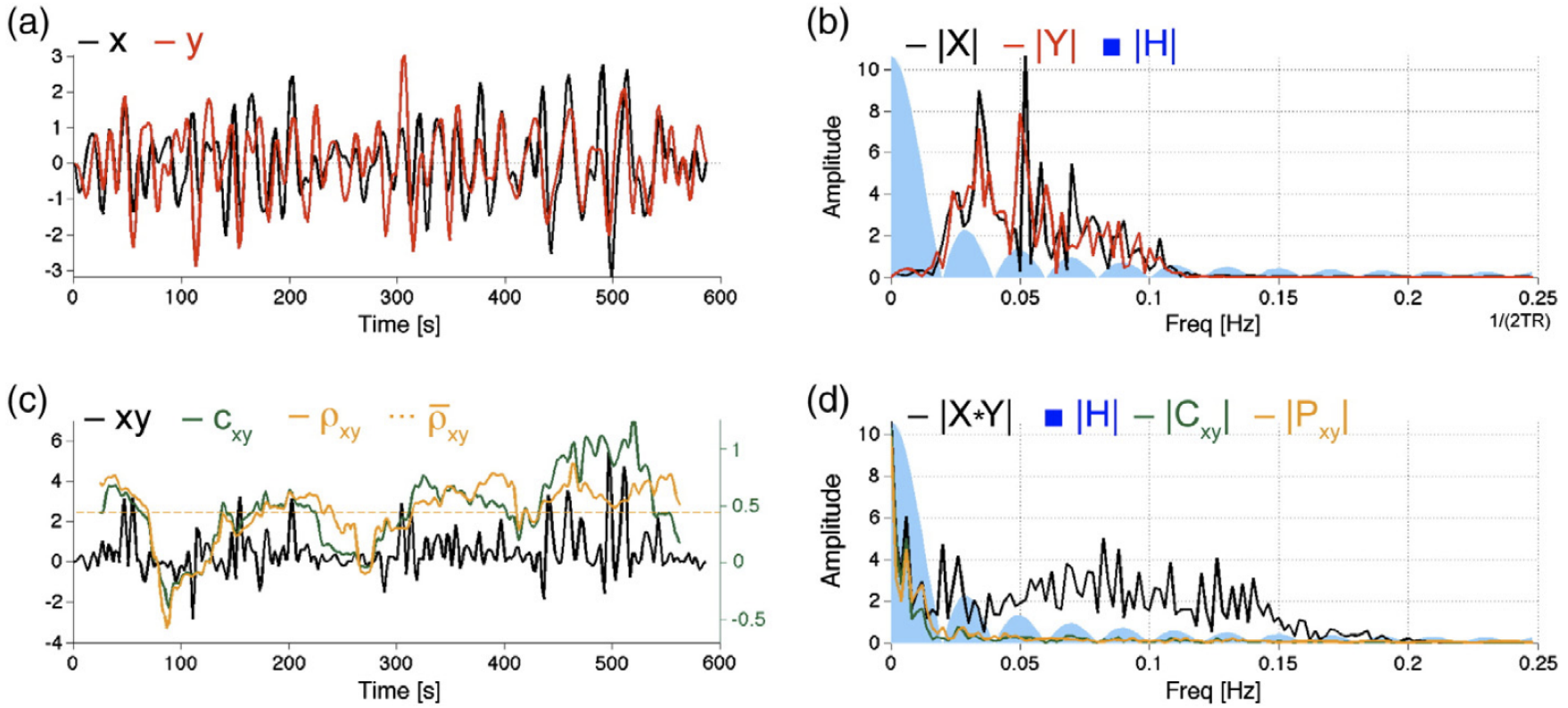


Window in Frequency Domain

Leonardi et al. NeuroImage, 2015

Sliding Window Correlation: Window Length vs. Amount of Fluctuation

WL = 50s ➔ $Fmin_{signals} = Fmax_{observedDynamicConn} = 0.02$ Hz



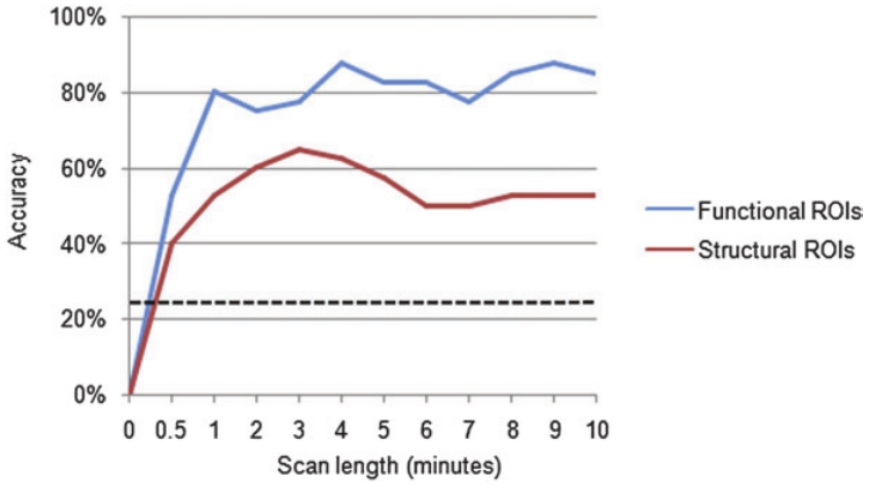
(1) Spurious fluctuations in dynFC can be limited by appropriate high pass filtering (1/WL).

(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.

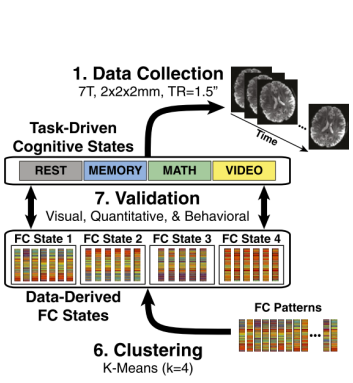
Leonardi et al. NeuroImage, 2015

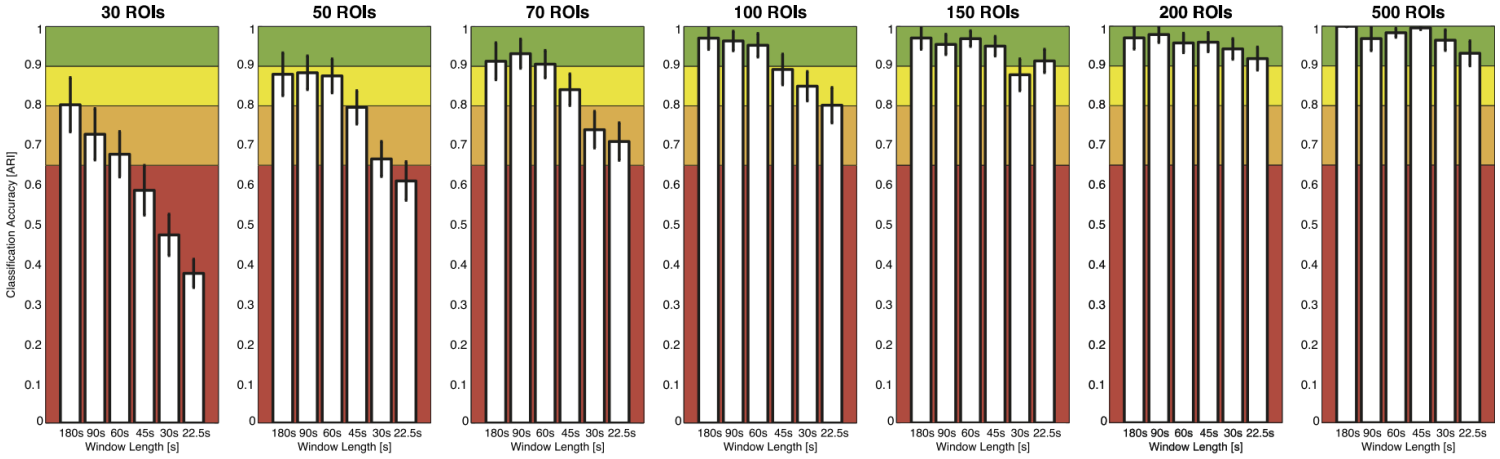
Functional Connectivity States: Parcellation Selection



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

Shirer et al. Cerebral Cortex 2012

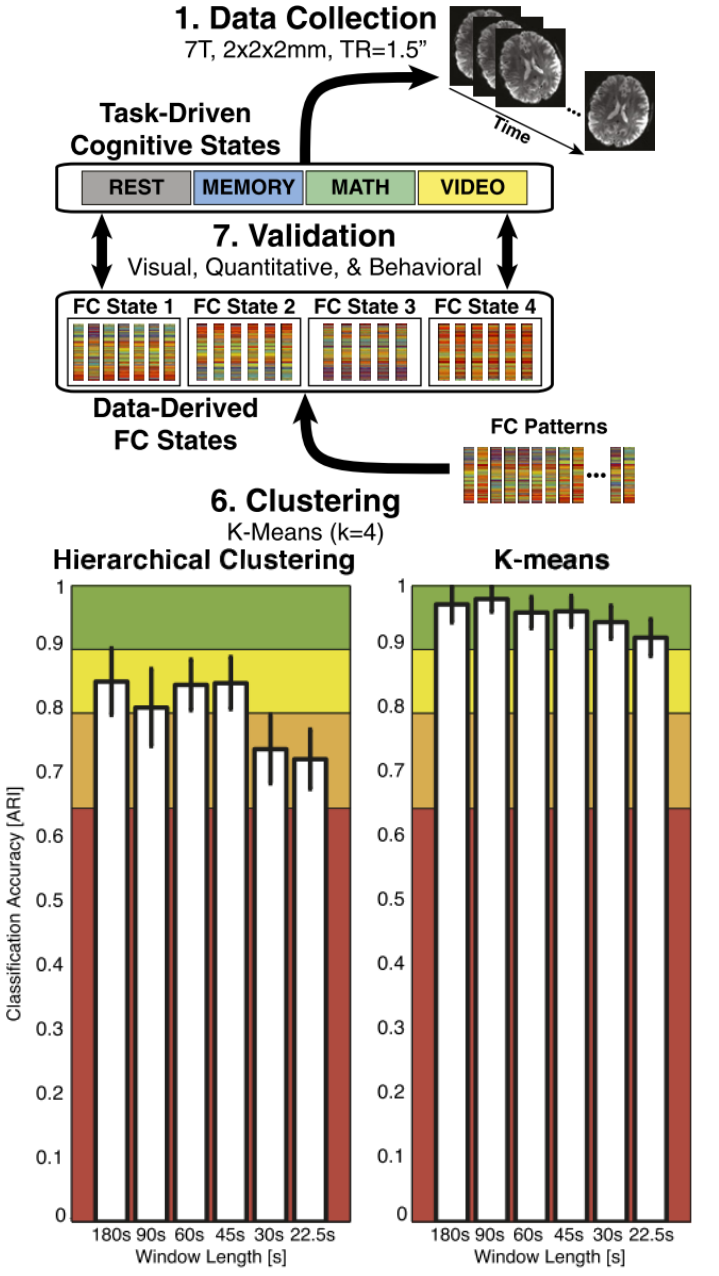




"More smaller ROIs" seem to perform better than "Less larger ROIS"

Gonzalez-Castillo et al., PNAS 2015

Functional Connectivity States: Clustering Algorithm



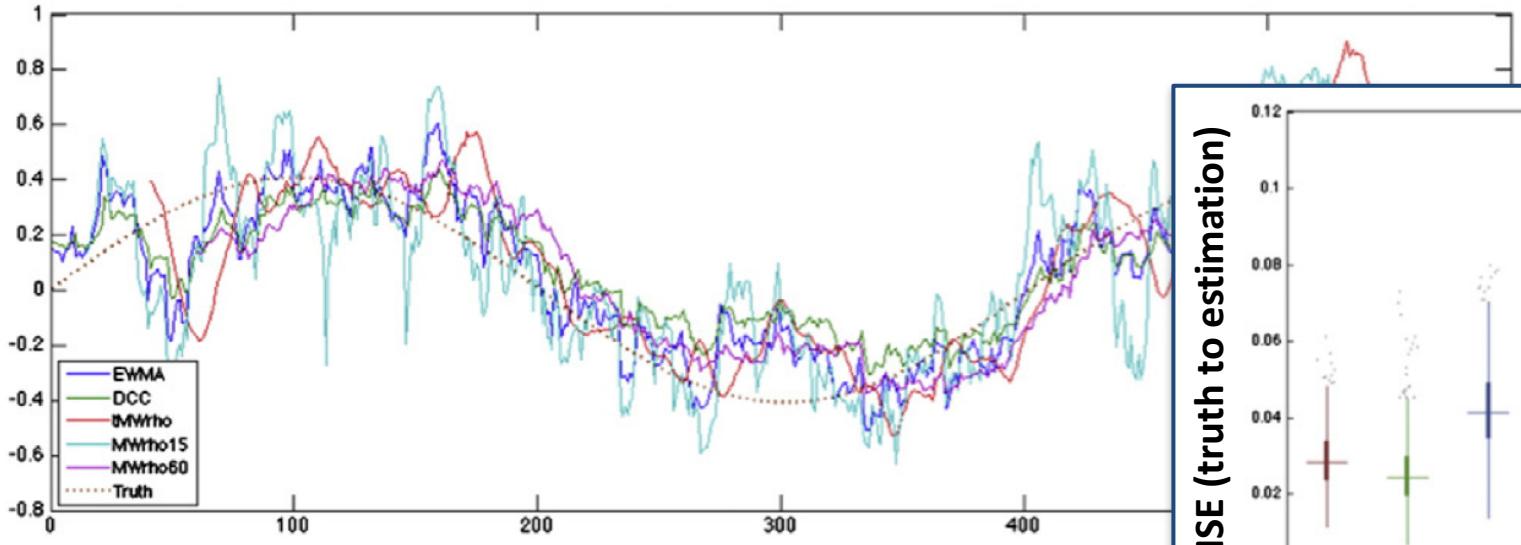
Gonzalez-Castillo et al., PNAS 2015

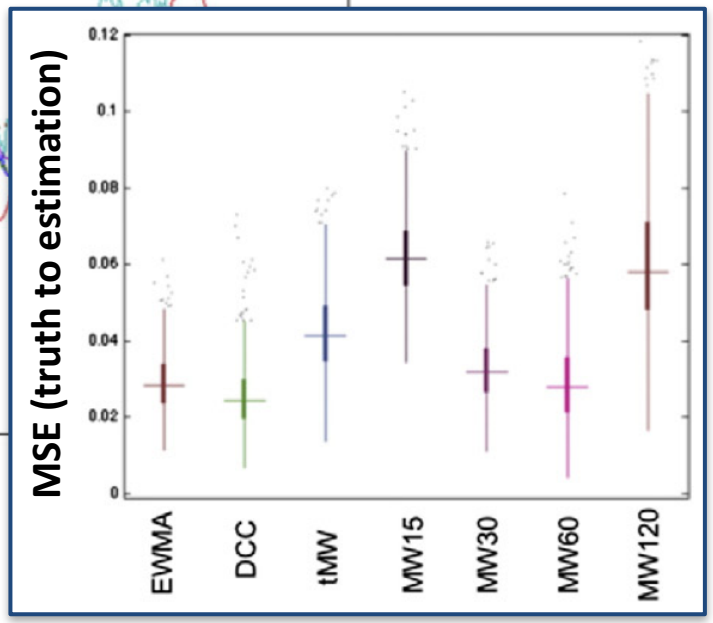
Other Methods: Dynamic Conditional Correlation (DCC) (I)

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.

Slowly-varying Periodic change in correlation





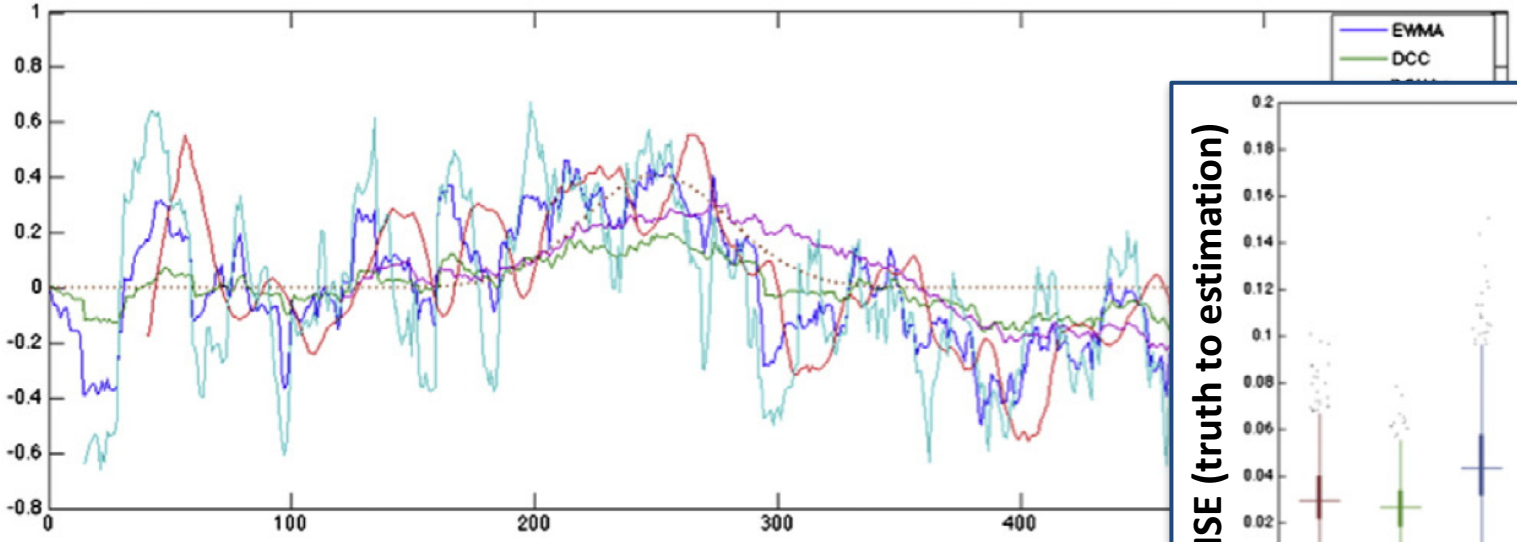
Linquist et al., NeuroImage, 2014

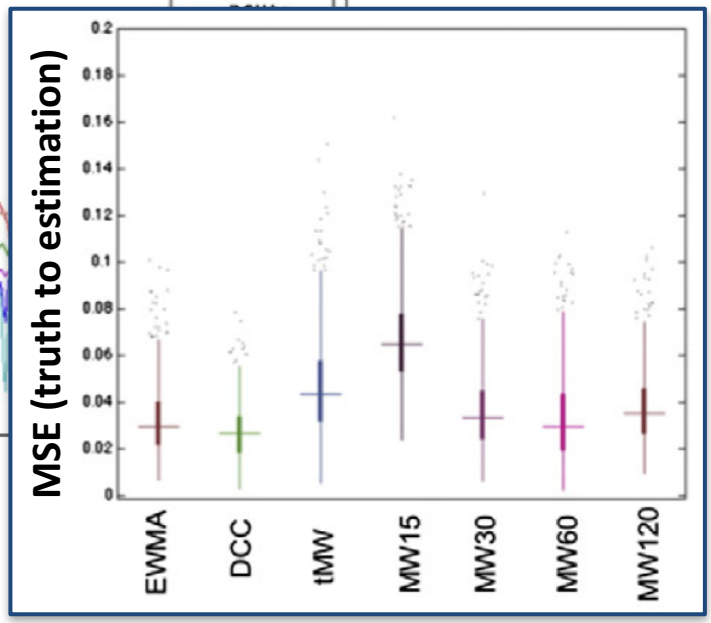
Other Methods: Dynamic Conditional Correlation (DCC) (II)

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



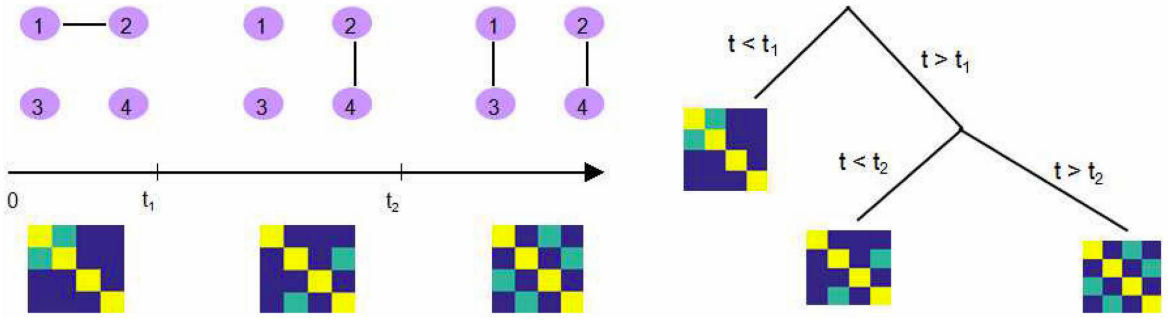


- Its ability to capture neuronal/cognitive meaningful fluctuations ought to be tested.
- Computation time increases linearly with number of ROIs.

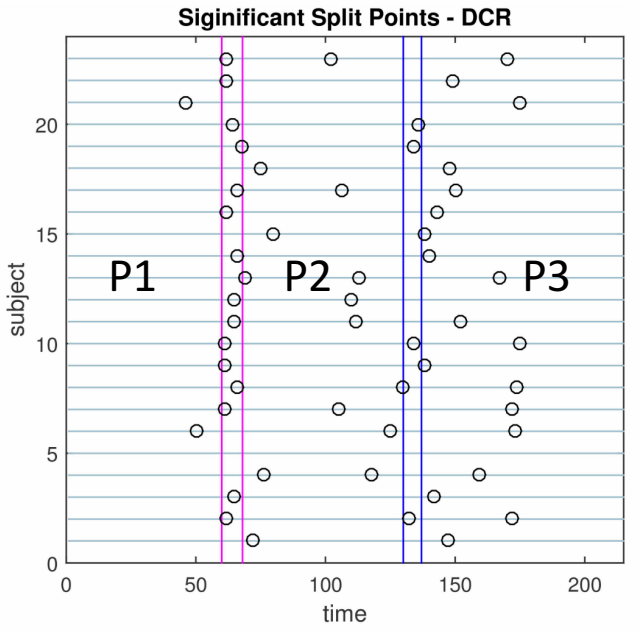
Linquist et al., NeuroImage, 2014

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

DCD: Data-driven technique to detect temporal change points in functional connectivity, and estimate FC patterns within each segment defined by the change points.



Test on Real Data: Social Evaluative Threat Experiment



Off-on-off design, with an anxiety-provoking speech preparation task sandwiched between two lower-anxiety rest periods.

- P1: No topic available yet.
- P2: Topic and instructions.
- P3: Subject is informed no speech needed.

Limitations:

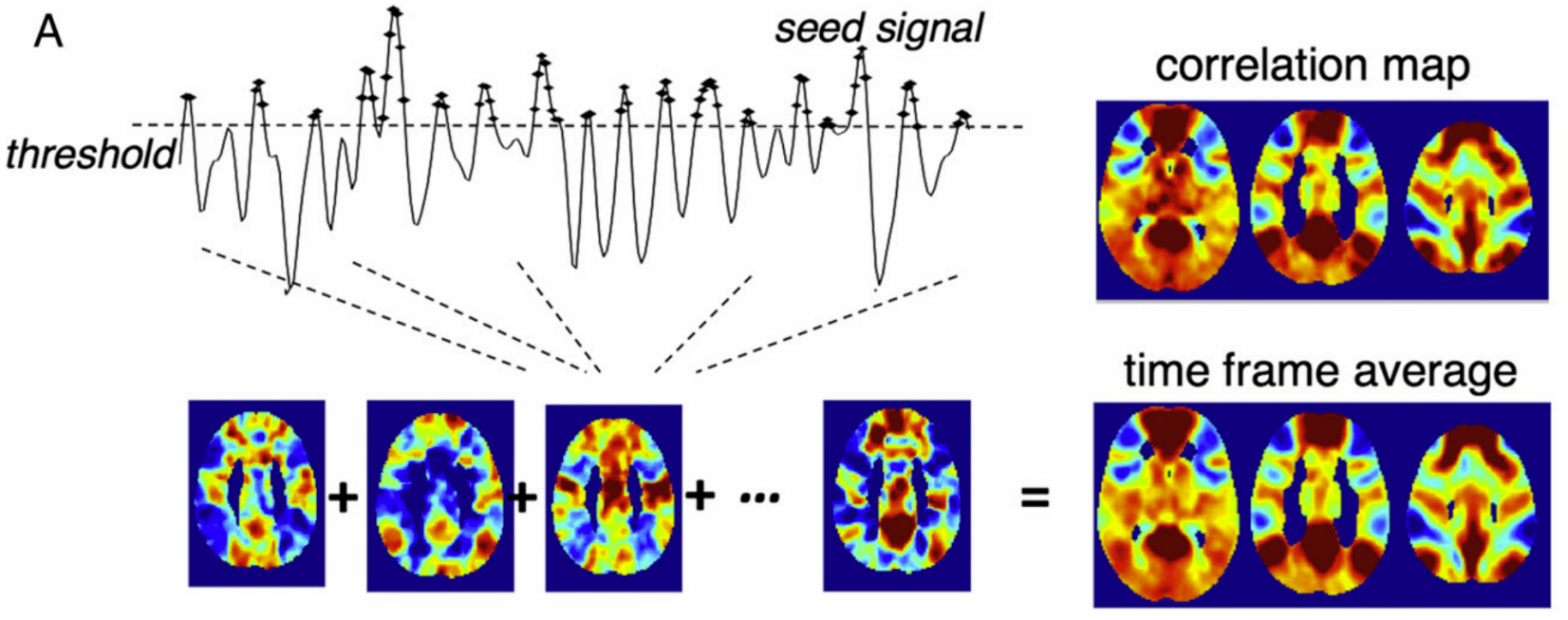
- Limited Number of ROIs
- Computationally expensive
- Five user parameters: min. distance between change points, significance level for bootstrapping, etc.

Xi & Linquist, Frontiers in Neuros., 2015

Other Methods: Frame-wise Analysis / Co-Activation Patterns

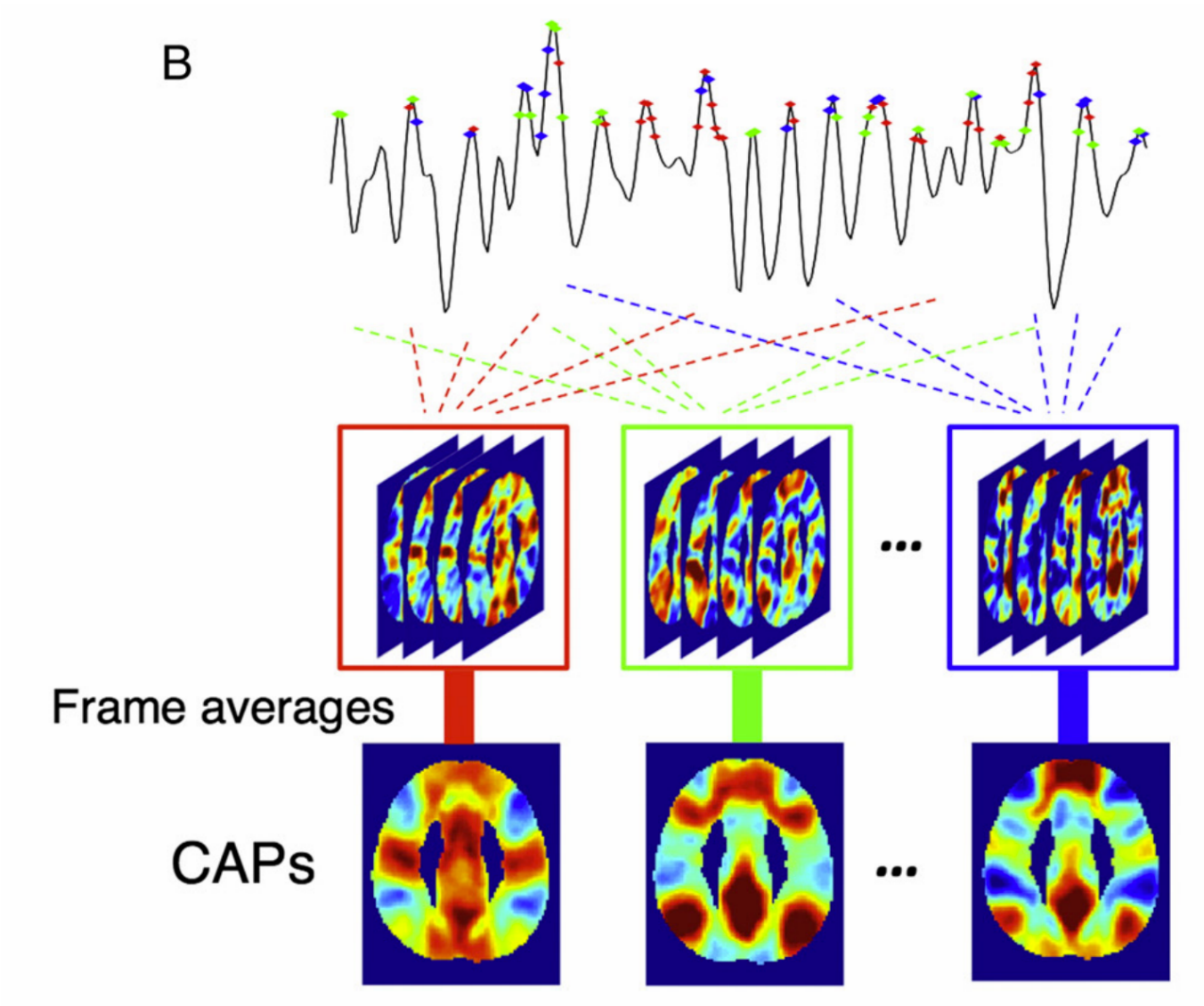
Sliding window assumes spontaneous brain activity is characterized by slow, but continuously evolving dynamics.

<u>Alternative</u>: all dynamic information is condensed into events/short periods. → Point Process Analysis [Tagliazucchi et al. 2010]



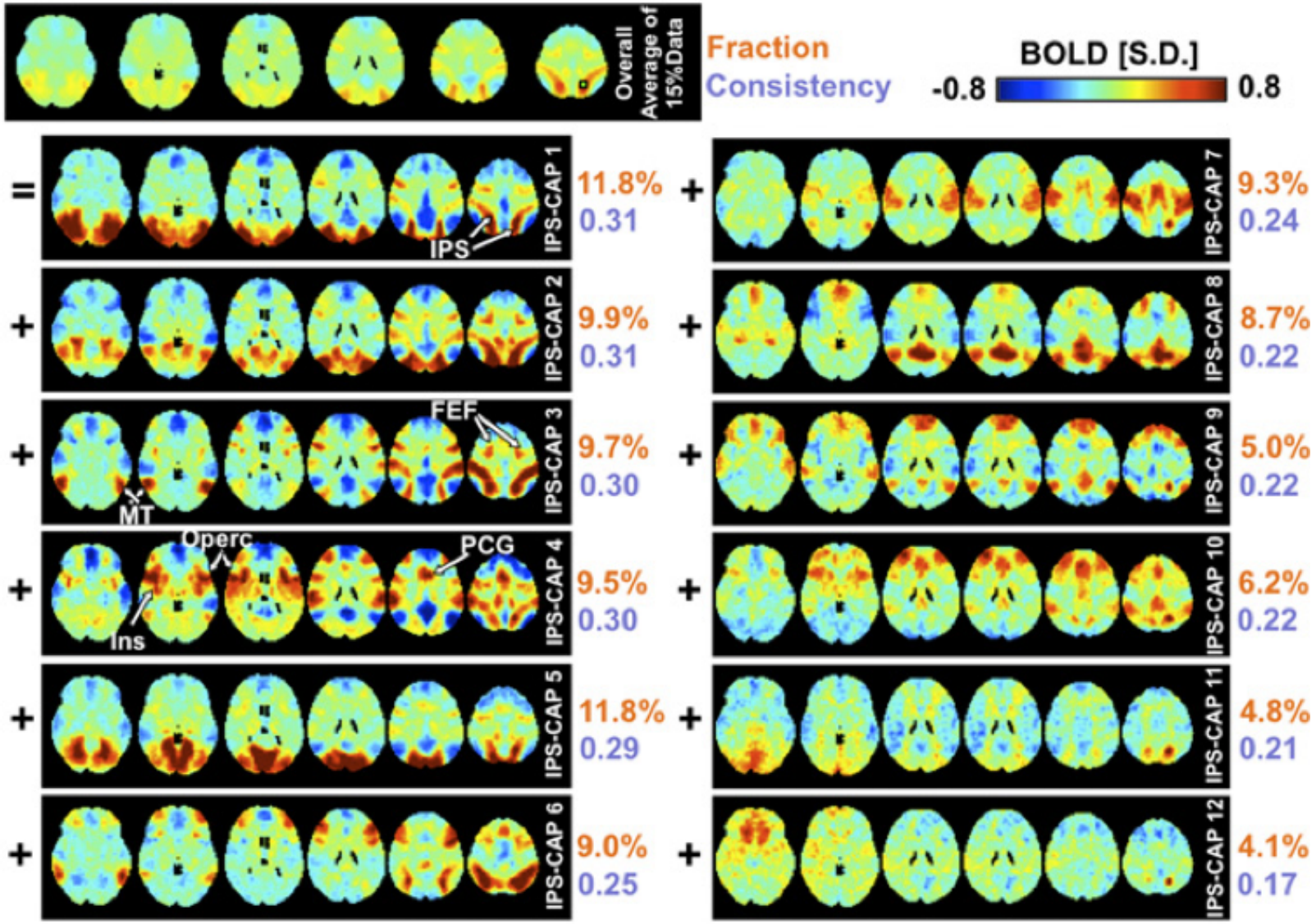
Lui et Dyun, PNAS, 2013; Chen et al. NeuroImage 2015

Other Methods: Frame-wise Analysis / Co-Activation Patterns



Lui et Dyun, PNAS, 2013; Chen et al. NeuroImage 2015

Other Methods: Frame-wise Analysis / Co-Activation Patterns



Example: Decomposition of the Dorsal Attention Network in 12 CAPS (seed in IPS) *Lui et Dyun, PNAS, 2013*

Other Methods…

Time – Frequency Analyses

- Chang, C., Glover, G.H., 2010. "Time-frequency dynamics of resting-state brain connectivity measured with fMRI". NeuroImage 50, 81–98
- Rack-Gomer, A.L., Liu, T.T., 2012. "Caffeine increases the temporal variability of resting- state BOLD connectivity in the motor cortex". NeuroImage 59, 2994–3002
- Demirtas, M., Tornador, C., et al. 2016. "Dynamic functional connectivity reveals altered variability in functional connectivity among patients with major depressive disorder". Hum. Brain Mapp. 37, 2918–2930.

Multiplication of Temporal Derivatives

- Shine, J.M., Koyejo, O., et al. 2015. "Estimation of dynamic functional connectivity using Multiplication of Temporal Derivatives". NeuroImage 122, 399–407.
- Shine, J.M., Koyejo, O., Poldrack, R.A., 2016. "Temporal metastates are associated with differential patterns of time-resolved connectivity, network topology, and attention." PNAS 113(35):9888-91.

Hidden Markov Models

- Eavani, H., Satterthwaite, T.D., Gur, R.E., Gur, R.C., Davatzikos, C., 2013. "Unsupervised learning of functional network dynamics in resting state fMRI". Brain 23, 426–437.

Dynamic Graph Analysis

- Betzel, R.F., Fukushima, et al. 2016. "Dynamic fluctuations coincide with periods of high and low modularity in resting-state functional brain networks". NeuroImage 127, 287–297.
- Sizemore & Bassett "Dynamic graph metrics: tutorial, toolbox and tale". NeuroImage [In Press]

Preti et al. NeuroImage 2016. Excellent review to look for an overview of methods

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.

Acknowledgements

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