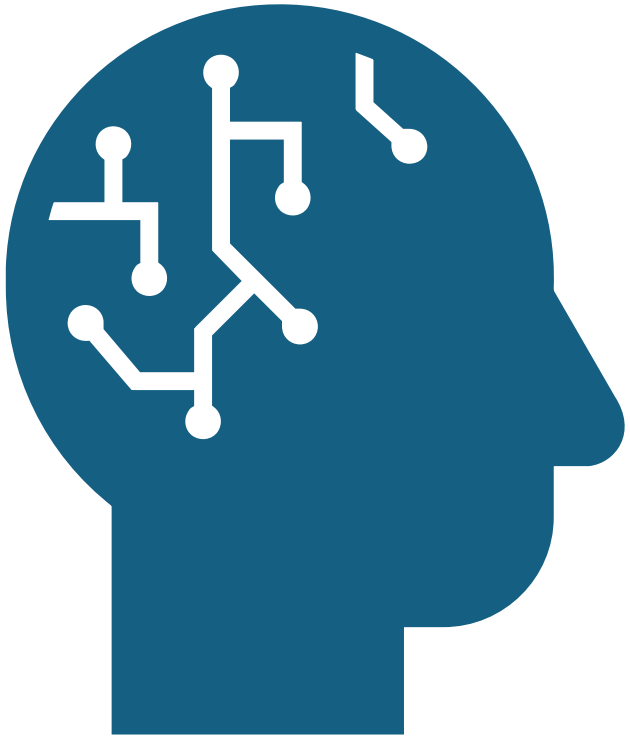


Functional Connectivity and Dynamic Connectivity

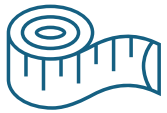
Javier Gonzalez-Castillo

Senior Associate Scientist, NIMH, NIH, Bethesda, MD

August 6th, 2024

Learning Objectives

Define Functional Connectivity



How to estimate Functional Connectivity

Static vs. Dynamic Functional Connectivity

How to estimate Dynamic Functional Connectivity

Special Considerations for task-based studies

What is “Functional Connectivity”?

◆ Human Brain Mapping 2:56–78(1994) ◆

Functional and Effective Connectivity in Neuroimaging: A Synthesis

Karl J. Friston

The MRC Cyclotron Unit, Hammersmith Hospital, London, England

Abstract: The brain appears to adhere to two principles of functional organization; *functional segregation* and *functional integration*. The integration within and between functionally specialized areas is mediated by *functional* or *effective connectivity*. The characterization of this sort of connectivity is an important theme in many areas of neuroscience. This article presents one approach that has been used in functional imaging.

What is “Functional Connectivity”?

Functional Connectivity

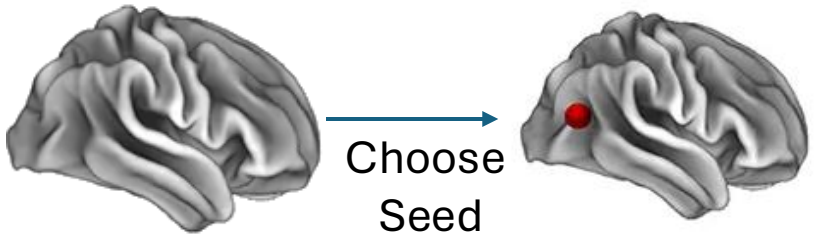
“temporal correlation between remote neurophysiological events”

“Functional connectivity is simply a statement about the observed correlations; it does not provide any direct insight into how these correlations are mediated. For example, at the level of multiunit microelectrode recordings, correlations can result from stimulus-locked transients, evoked by a common afferent input, or reflect stimulus-induced oscillations, phasic coupling of neural assemblies, mediated by synaptic connection”

Effective Connectivity

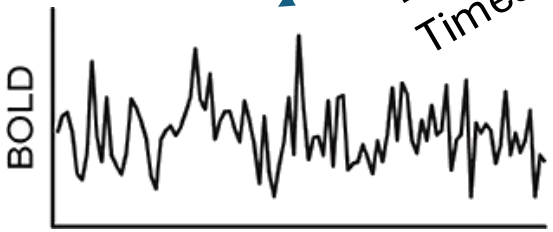
“the influence one neural system exerts over another”

How to estimate functional connectivity: Seed-based Correlation

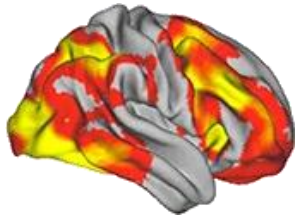


Choose Seed

Extract Timeseries

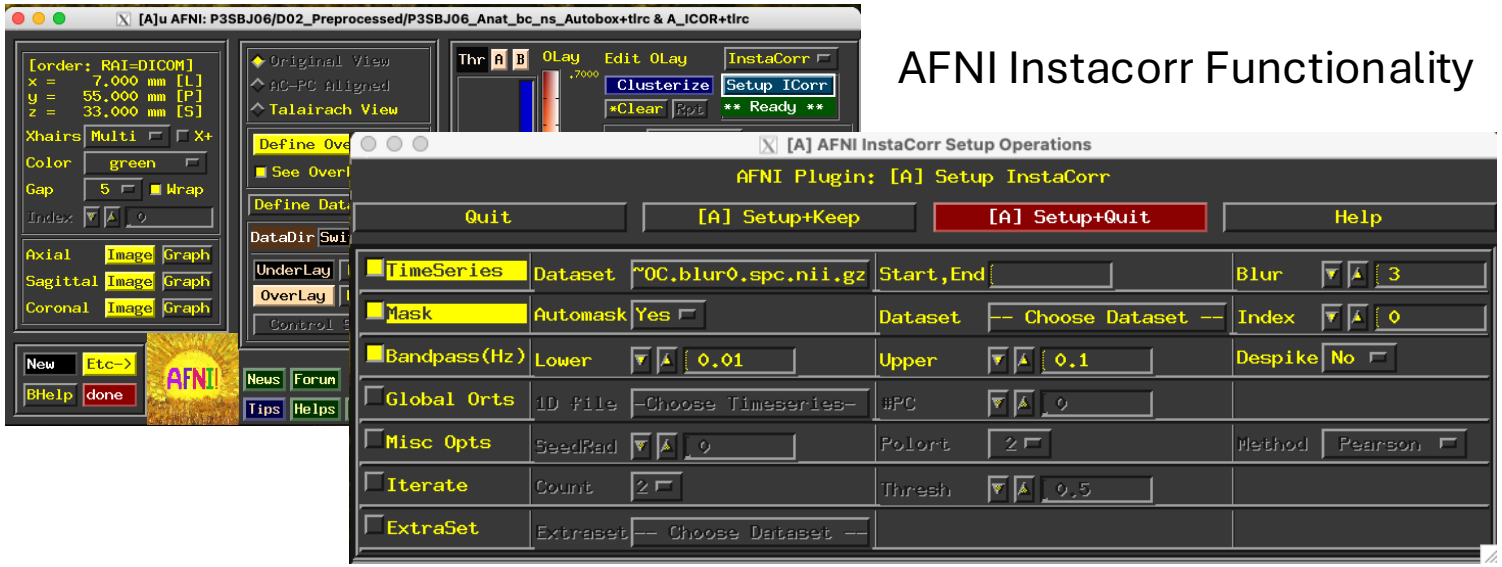


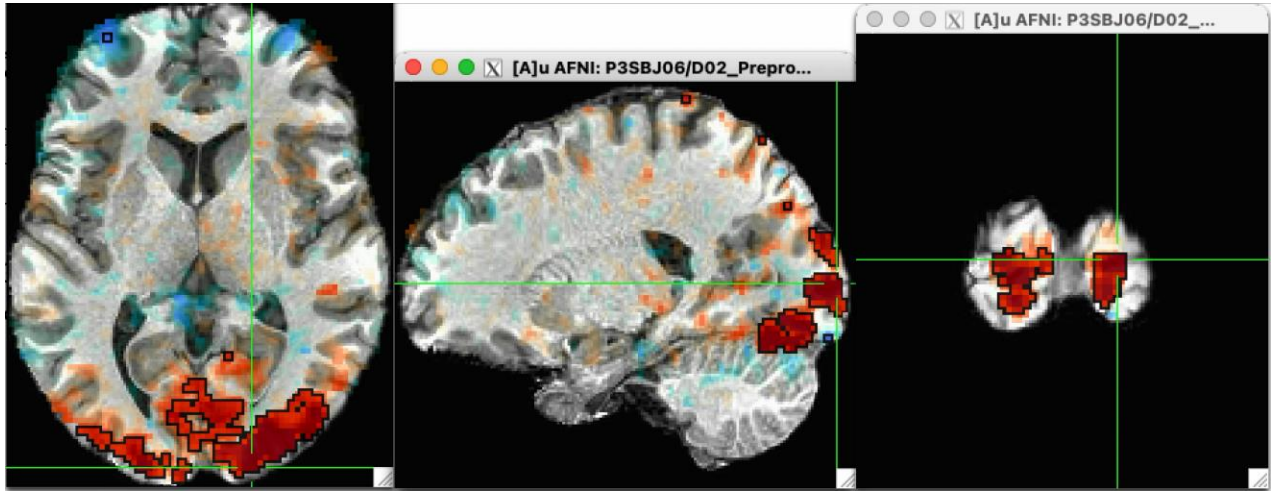
Correlate across the brain



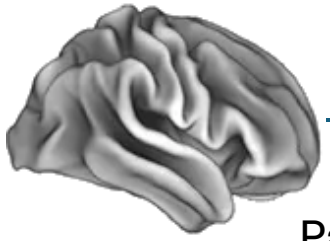
https://anastasija-v-petrovic.medium.com/an-overview-of-functional-connectomics-resting-state-fmri-8aca8b2446cb

AFNI Instacorr Functionality

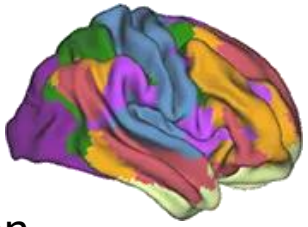




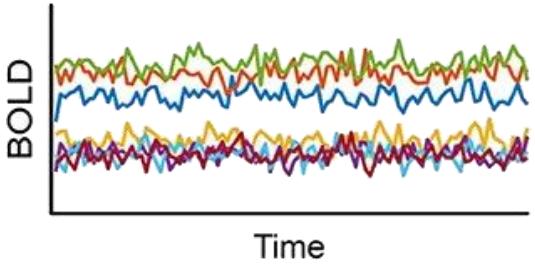
How to estimate functional connectivity: Seed-based Correlation



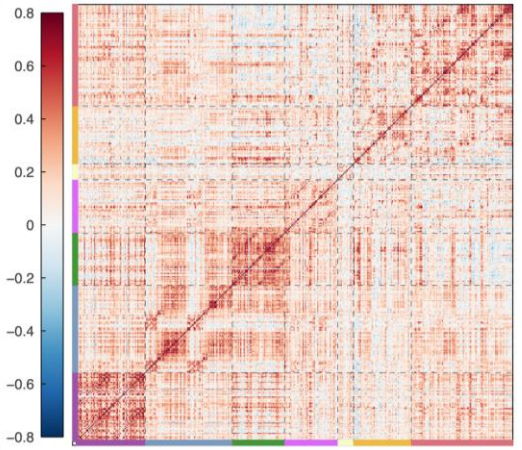
Choose Parcellation



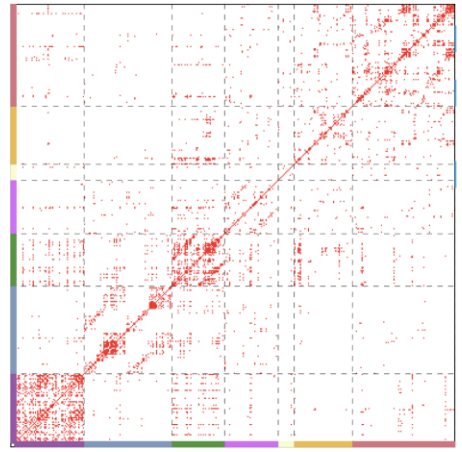
Extract Timeseries



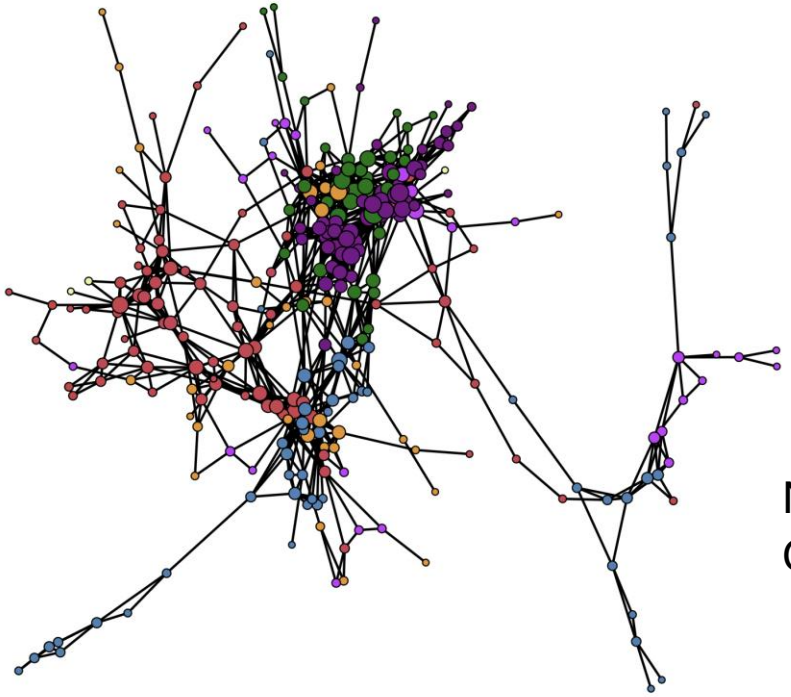
Compute Pair-wise Correlation

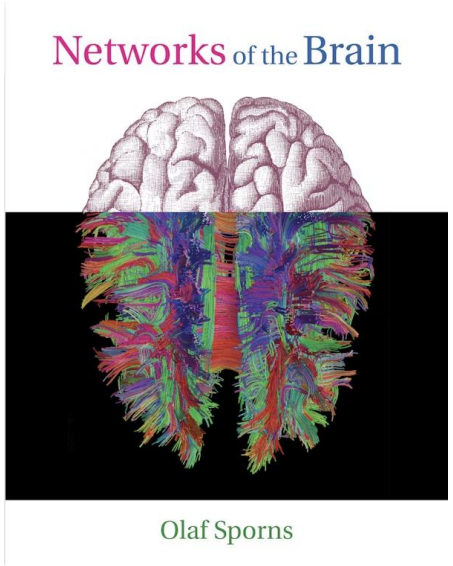


Threshold

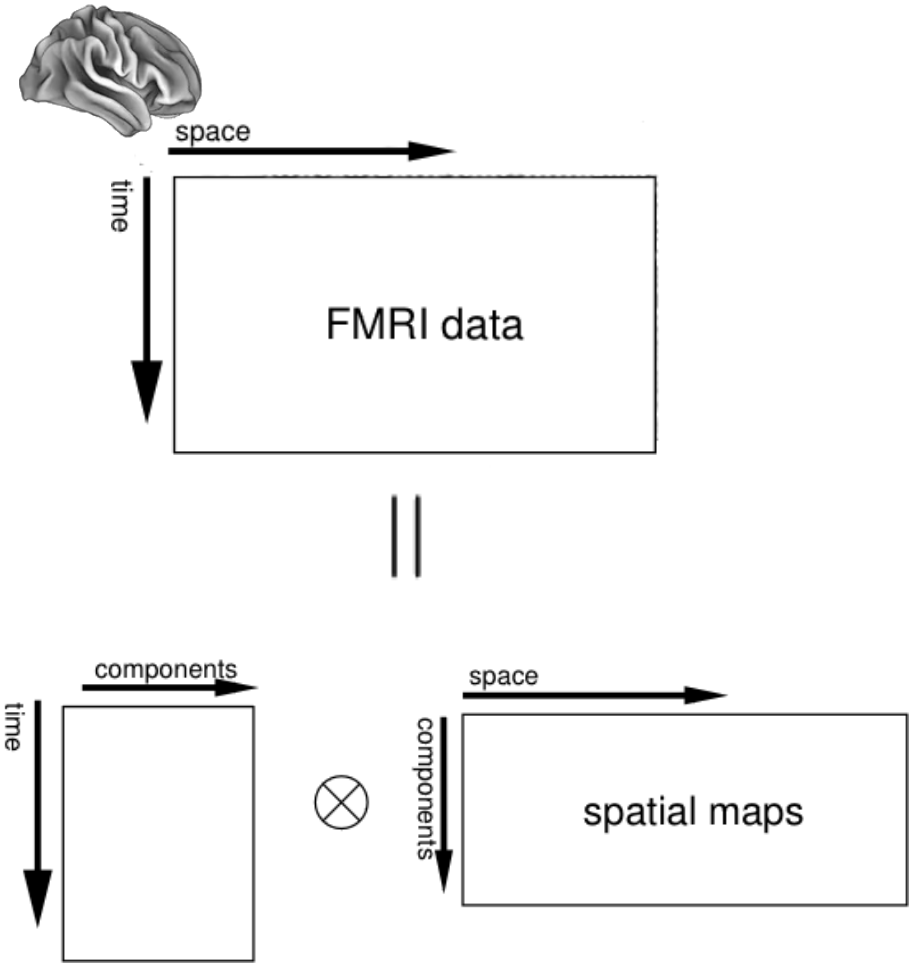


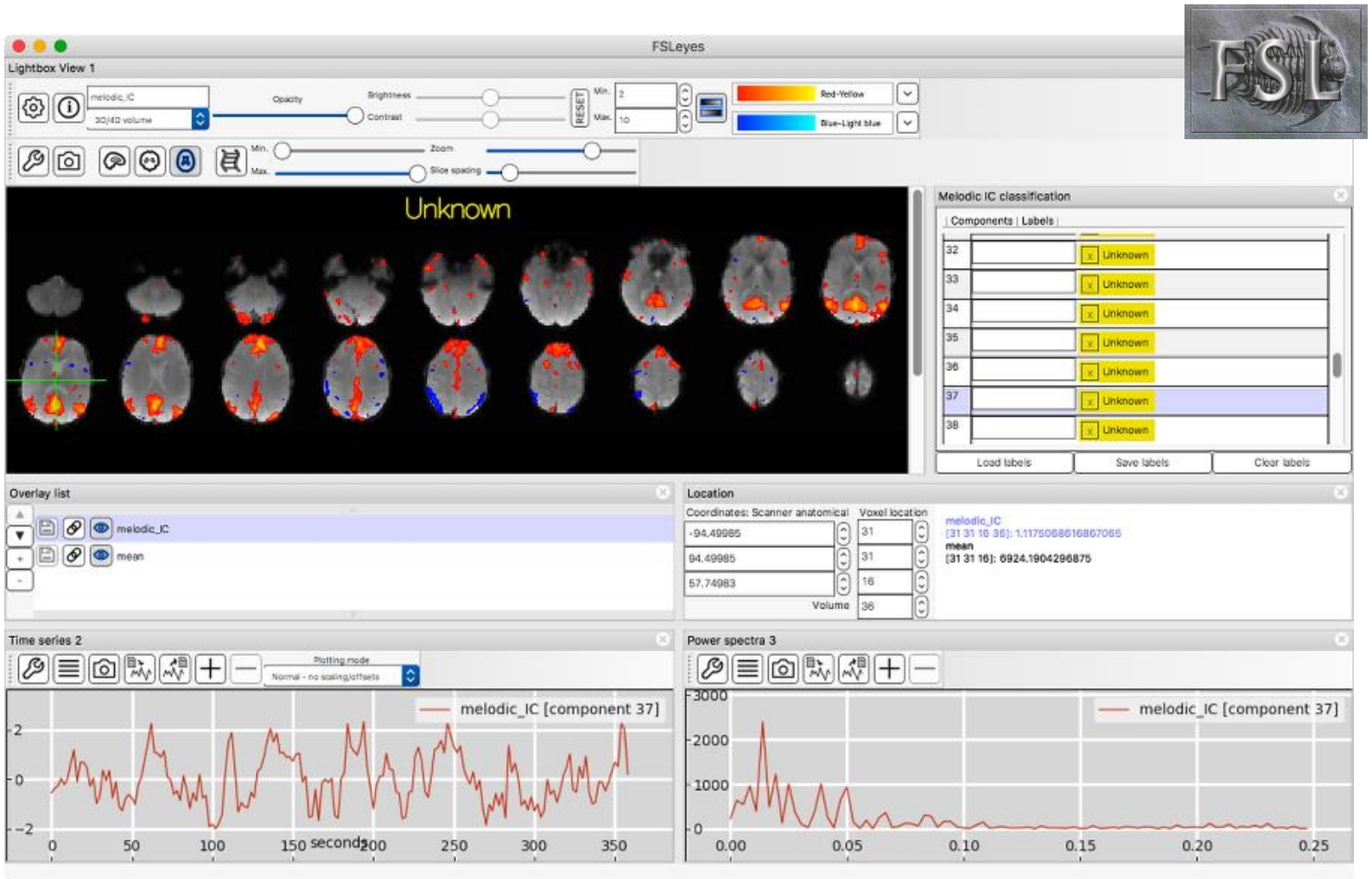
Model as Graph





How to estimate functional connectivity: ICA

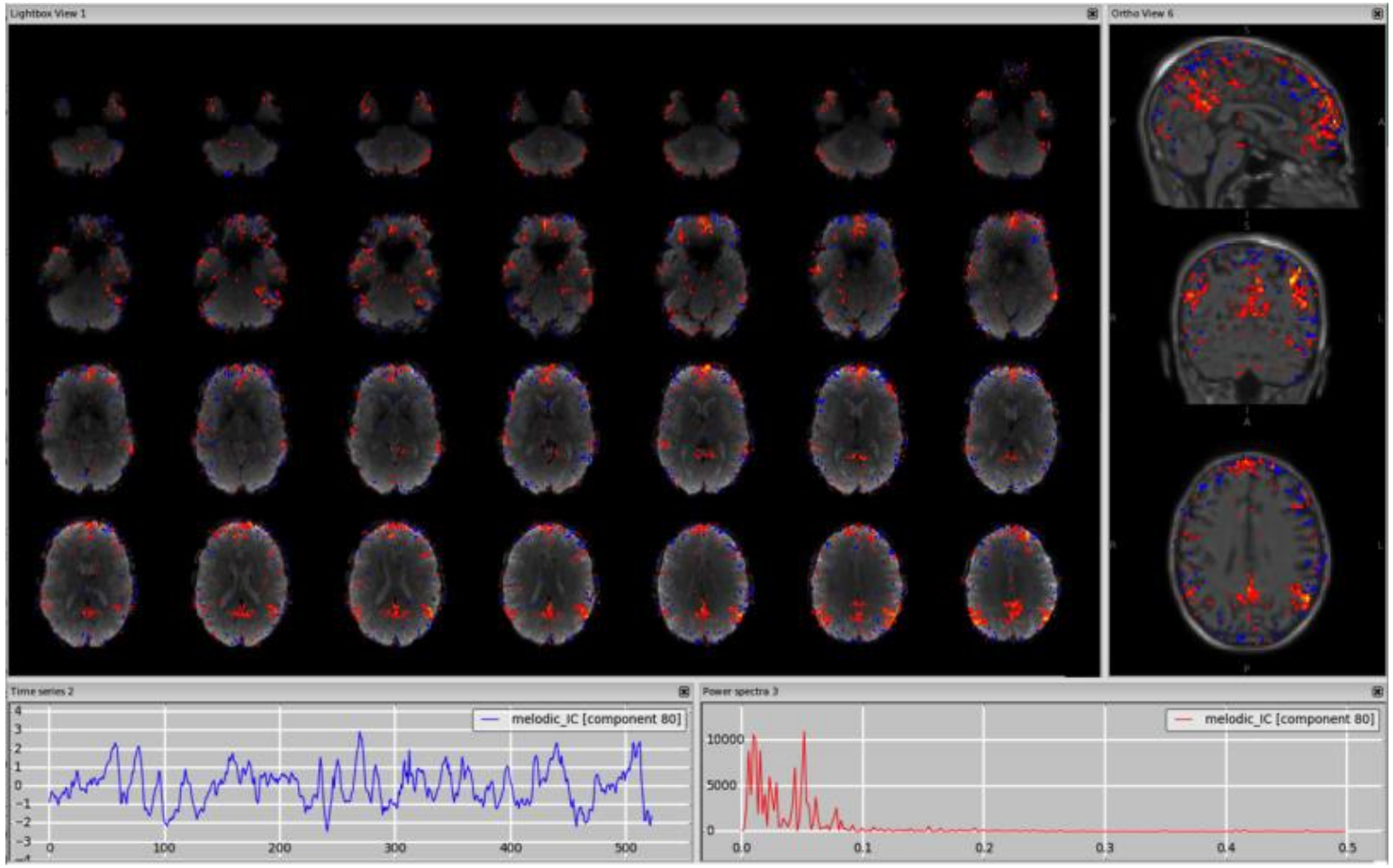




Beckmann et al. “Probabilistic Independent Component Analysis for functional magnetic resonance Imaging” IEEE Trans. Med. (20 04)

How to estimate functional connectivity: ICA

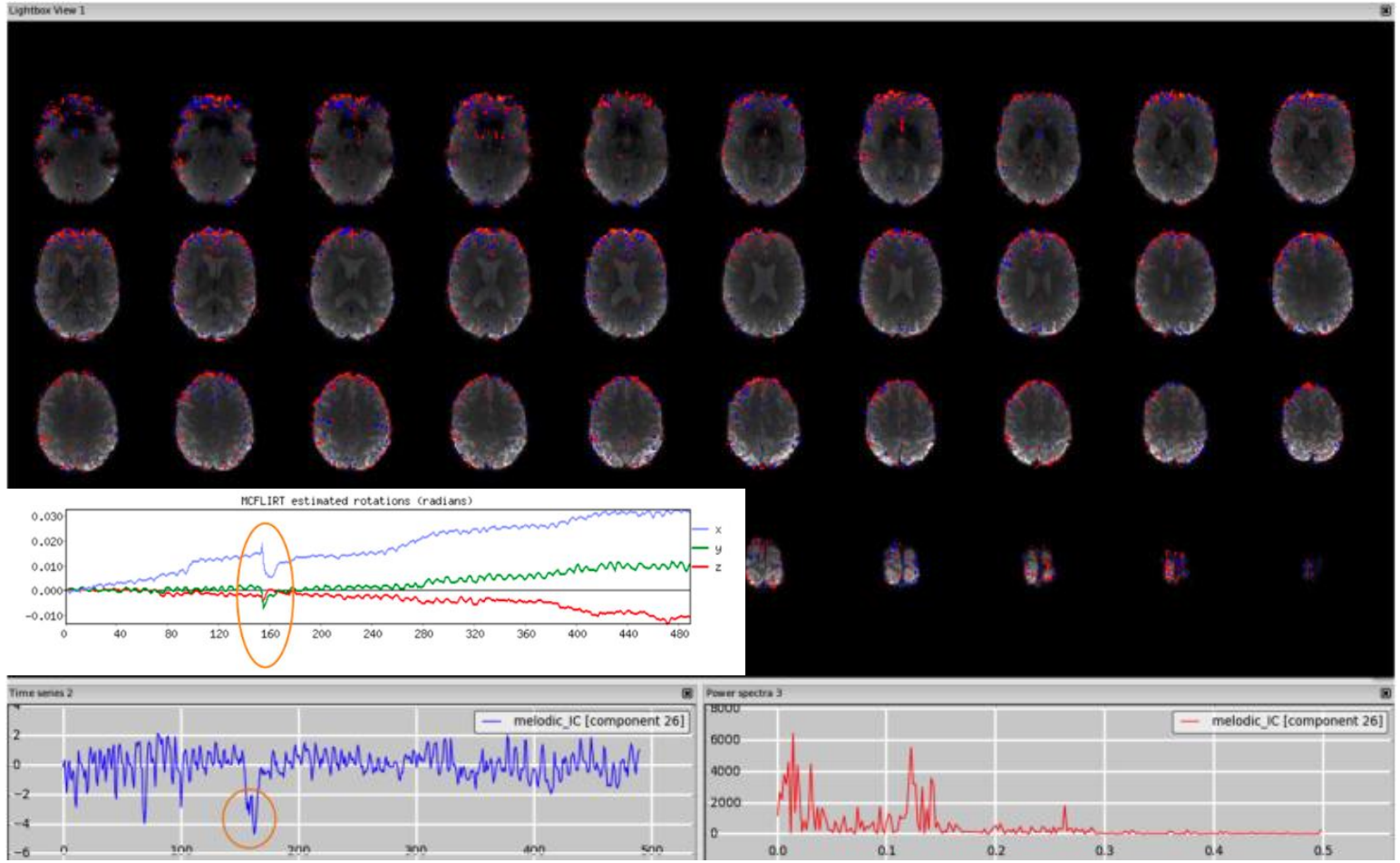
DEFAULT MODE NETWORK



Smith et al. “Hand classification of fMRI ICA noise components” NeuroImage (2017)

How to estimate functional connectivity: ICA

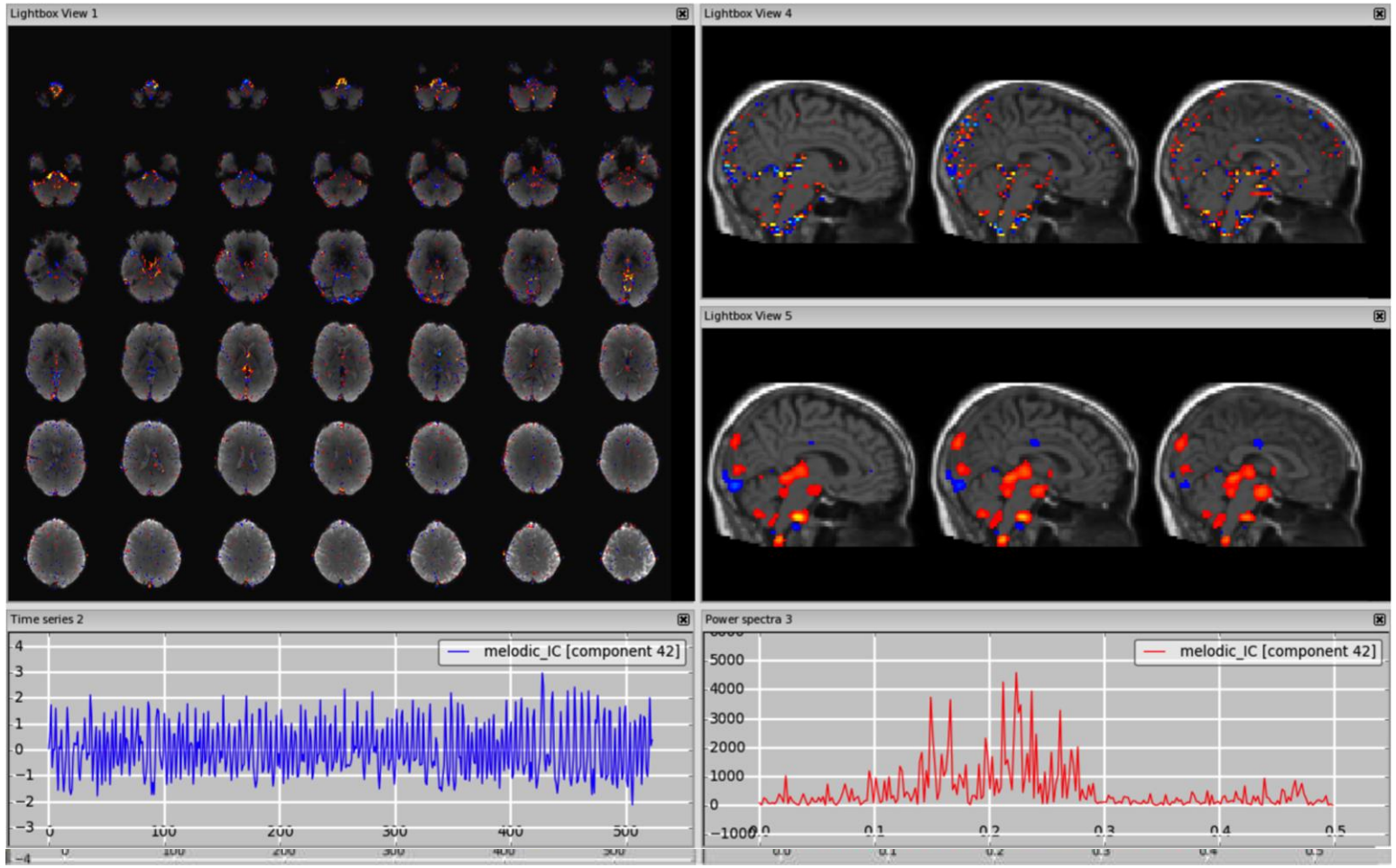
HEAD MOTION



Smith et al. “Hand classification of fMRI ICA noise components” NeuroImage (2017)

How to estimate functional connectivity: ICA

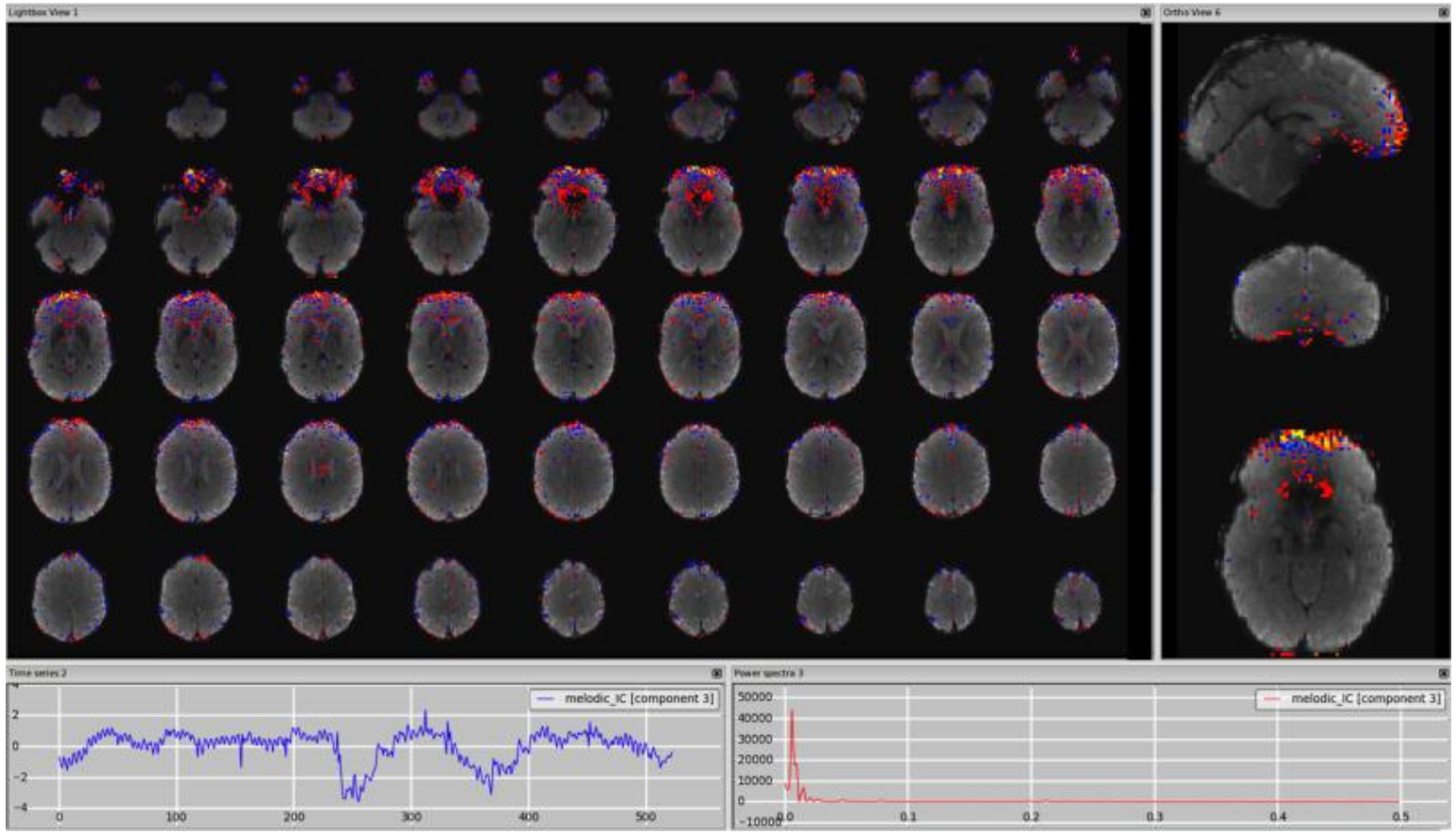
CEREBROSPINAL FLUID PULSATIONS



Smith et al. “Hand classification of fMRI ICA noise components” NeuroImage (2017)

How to estimate functional connectivity: ICA

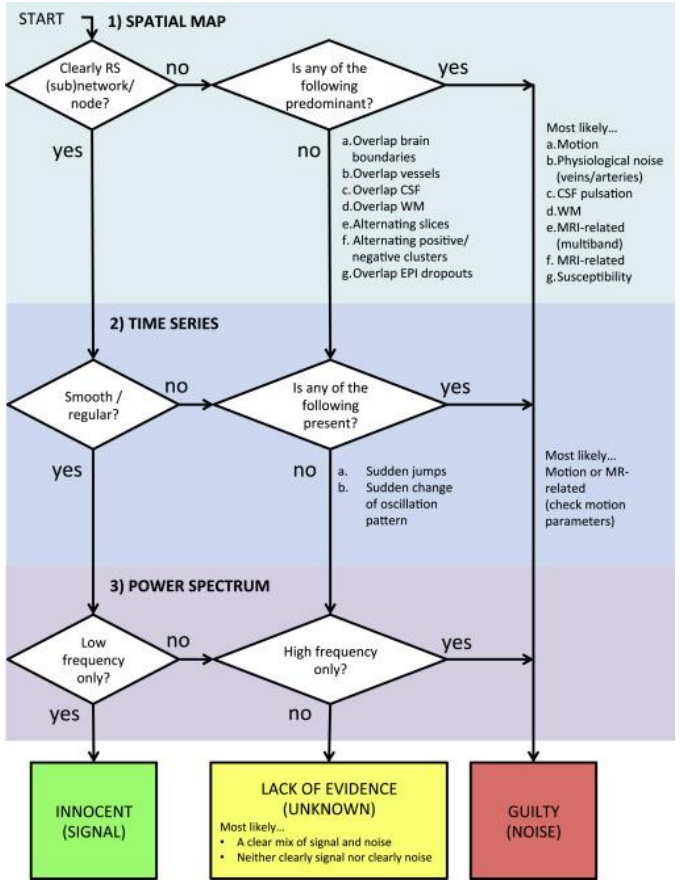
SUSCEPTIBILITY ARTIFACT



Smith et al. “Hand classification of fMRI ICA noise components” NeuroImage (2017)

How to estimate functional connectivity: ICA

Manual Classification



Smith et al. “Hand classification of fMRI ICA noise components” NeuroImage (2017)

Single Echo Automatic Classification

ELSEVIER

NeuroImage

Volume 112, 15 May 2015, Pages 267-277

ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data

Raimon H.R. Pruim [a b], Maarten Mennes [a b], Daan van Rooij [b c], Alberto Llera [b], Jan K. Buitelaar [a b d], Christian F. Beckmann [a b e]

ELSEVIER

NeuroImage

Volume 90, 15 April 2014, Pages 449-468

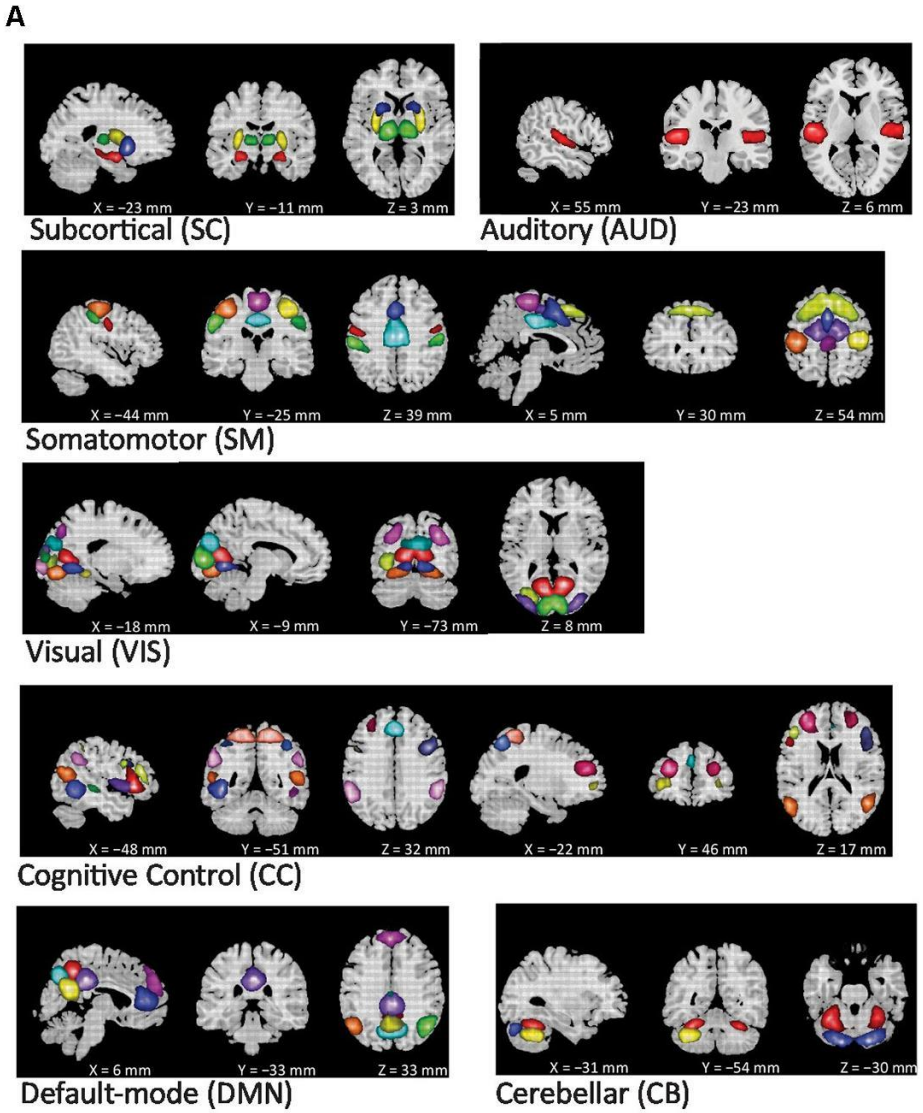
Automatic denoising of functional MRI data: Combining independent component analysis and hierarchical fusion of classifiers

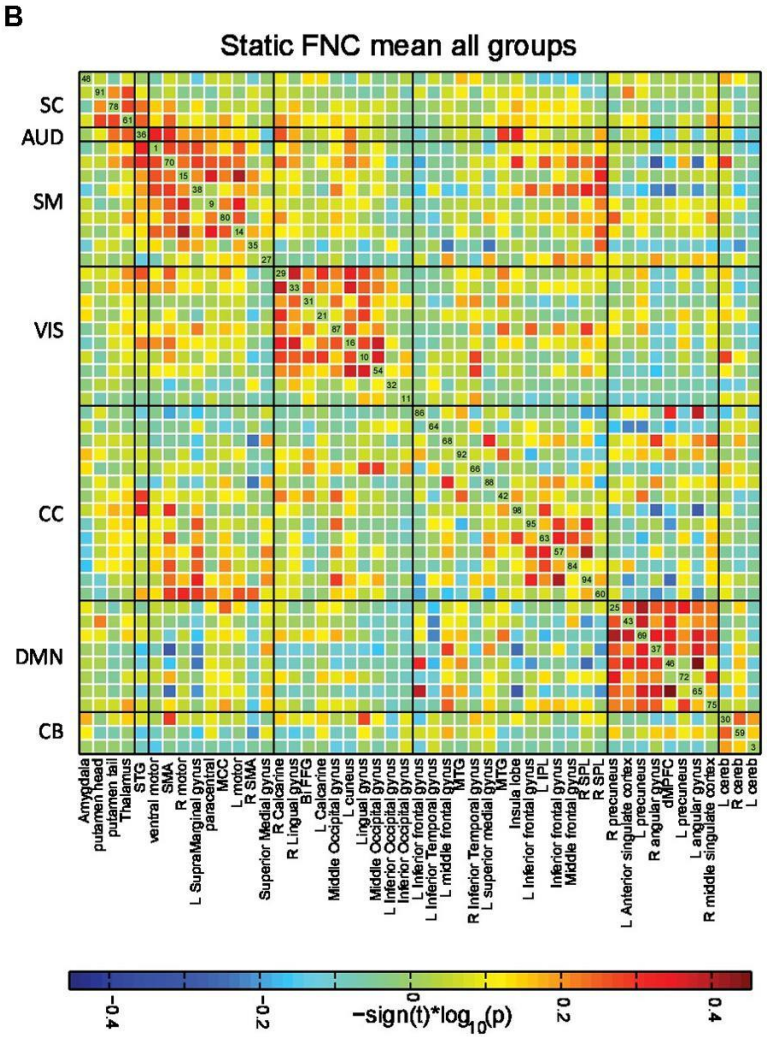
Gholamreza Salimi-Khorshidi [a], Gwenaëlle Douaud [a], Christian F. Beckmann [b c], Matthew F. Glasser [d], Ludovica Griffanti [a e f], Stephen M. Smith [a]

Multi Echo Automatic Classification

tedana

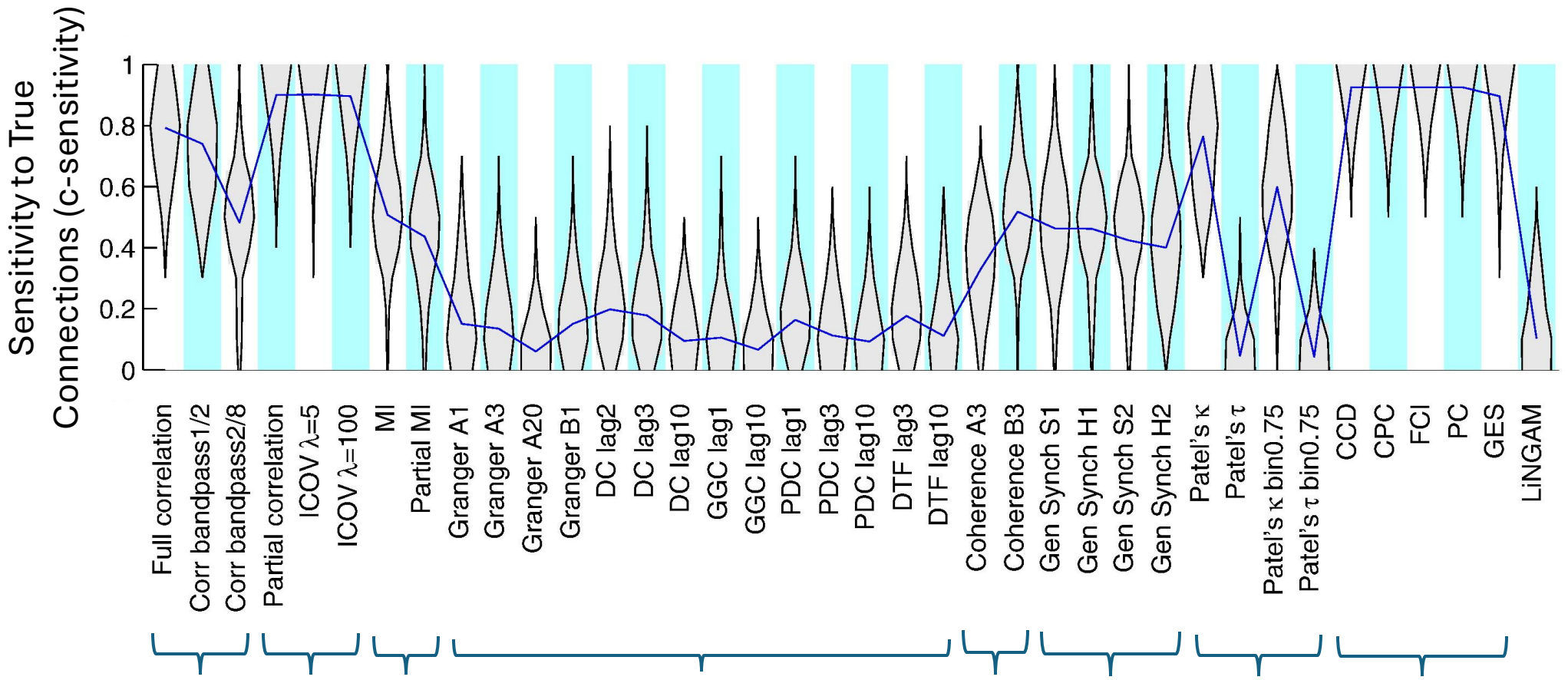
How to estimate functional connectivity: ICA





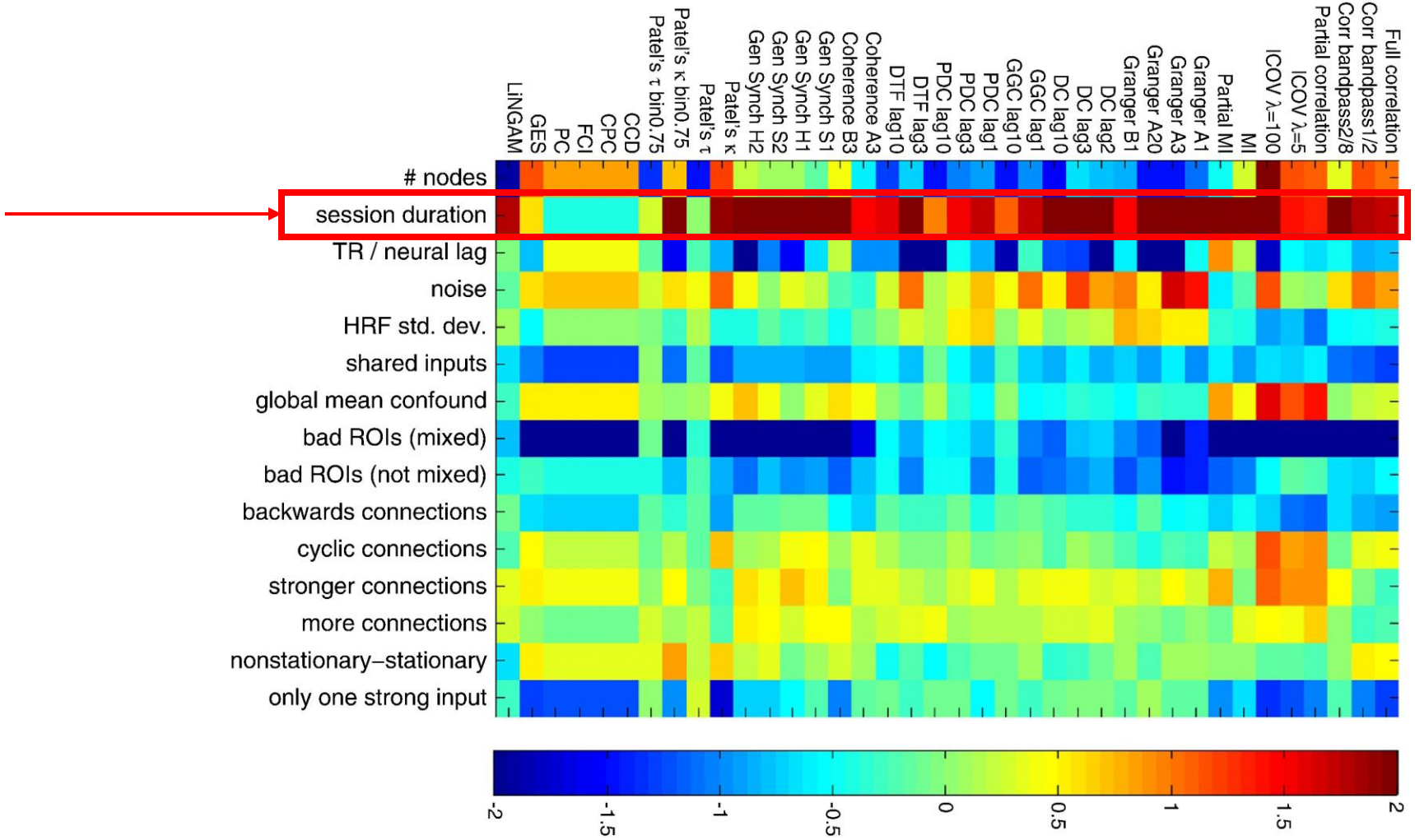
Rashid et al. Frontiers in Neuroscience (2014)

How to estimate functional connectivity: Other metrics



Smith et al. "Network modelling methods for fMRI" NeuroImage (2011)

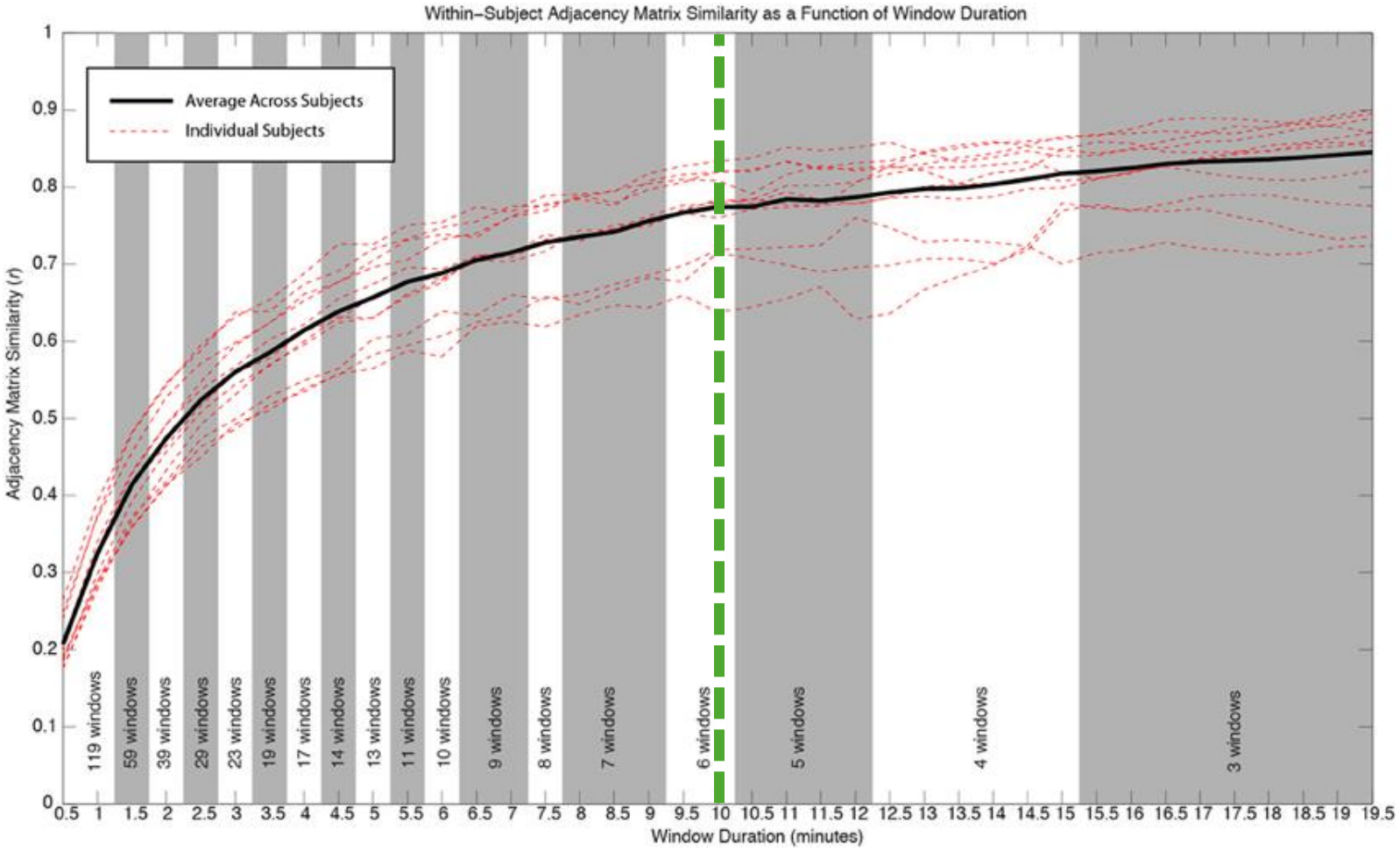
How to estimate functional connectivity: Scan length?



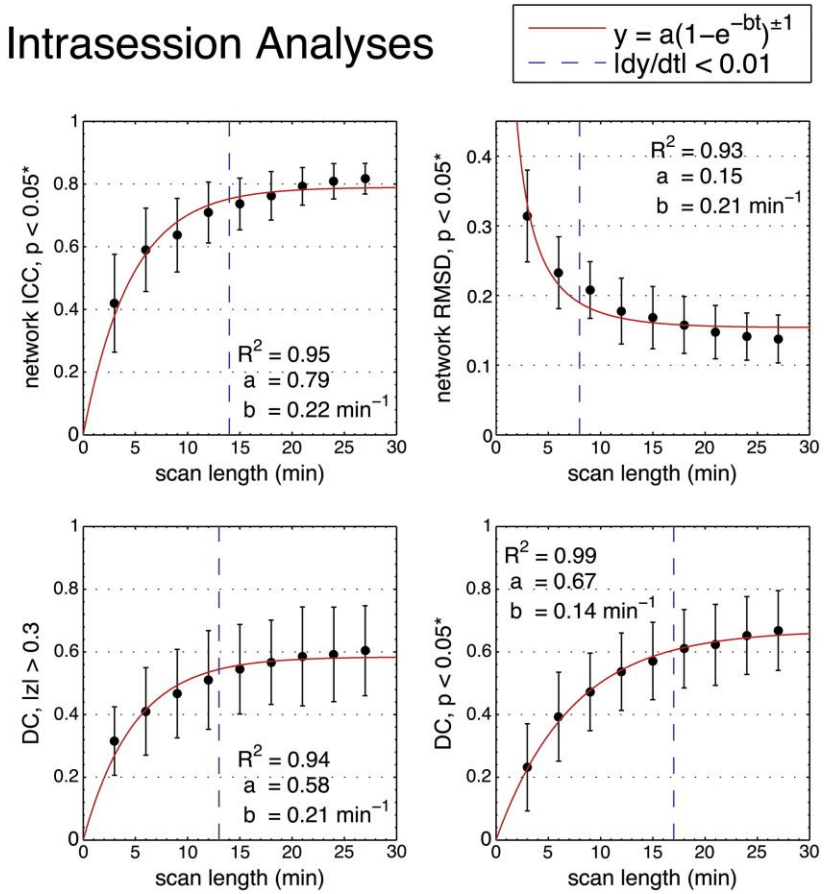
Minimum Recommended Duration: 10 mins

Smith et al. “Network modelling methods for fMRI” NeuroImage (2011)

How to estimate functional connectivity: Scan length?



Gonzalez-Castillo et al. "The spatial structure of resting state connectivity stability on the scale of minutes" Front. Neurosci. (2014)

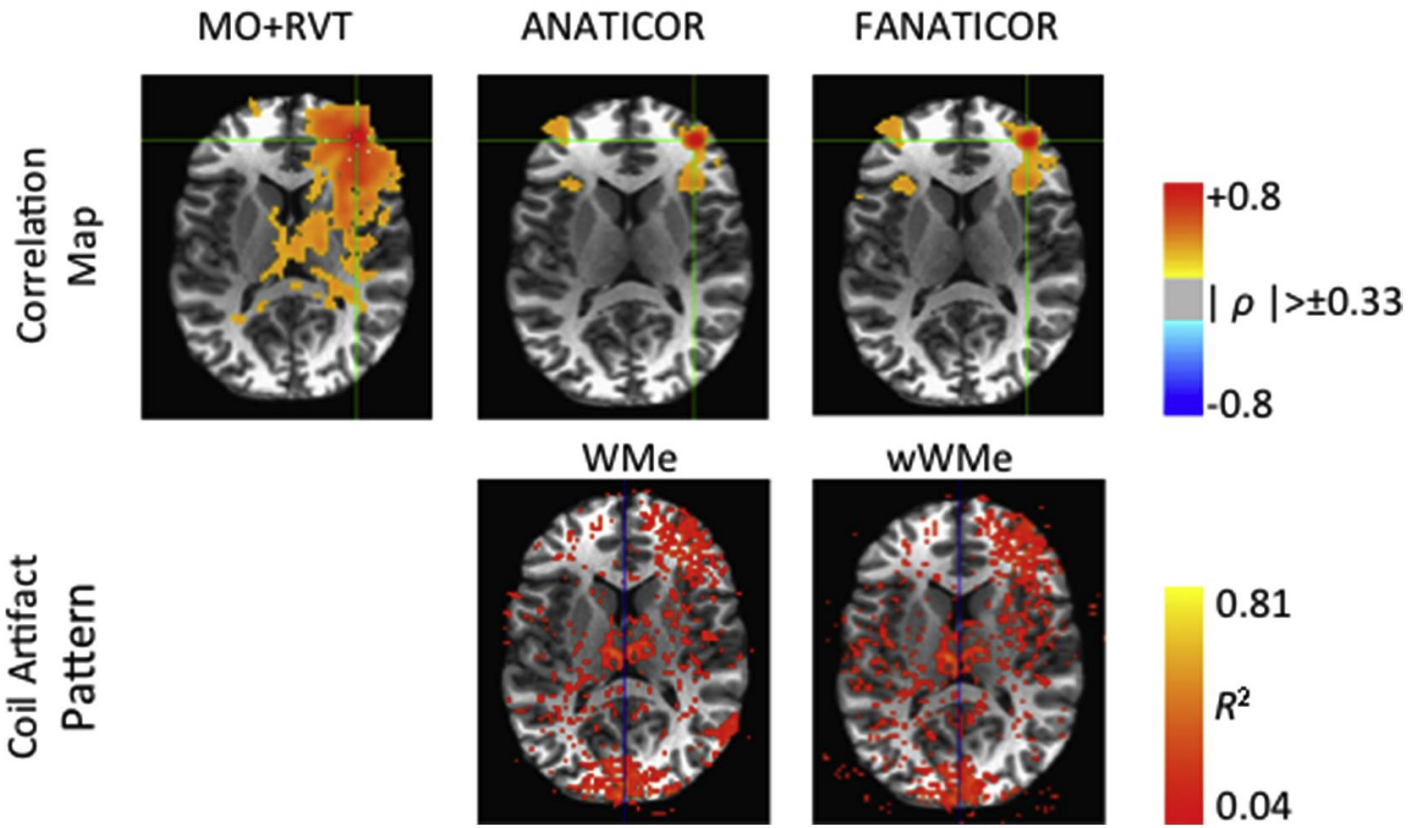


Birn et al. "The effect of scan length on the reliability of rsfMRI connectivity estimates" NeuroImage (2013)

How to estimate functional connectivity: pay special attention to confounds with spatial structure

Hardware

Slow Drifts, Thermal Noise, Coil Instabilities



Jo et al. "Fast detection and reduction of local transient artifacts in resting-state fMRI" Computer in Biology and Medicine (2020)

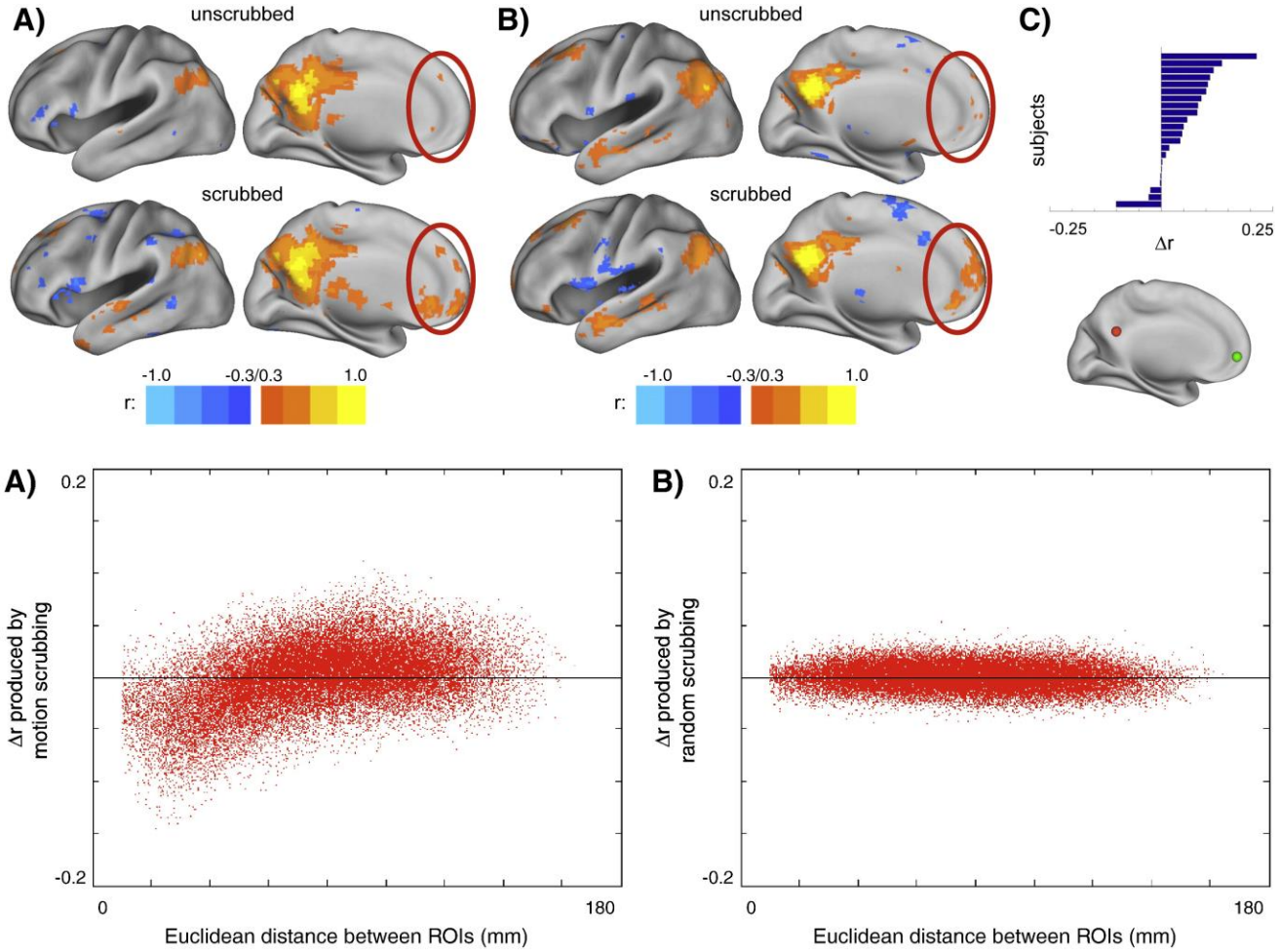
How to estimate functional connectivity: pay special attention to confounds with spatial structure

Hardware

Slow Drifts, Thermal Noise, Coil Instabilities

Participant

Head Motion → ↓ Long Distance FC, ↑ Short Distance FC



Power et al. "Spurious but systematic correlations in FC MRI networks arise from subject motion" NeuroImage (2012)

How to estimate functional connectivity: pay special attention to confounds with spatial structure

Hardware

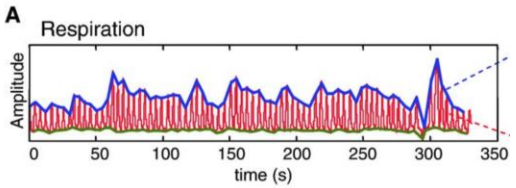
Slow Drifts, Thermal Noise, Coil Instabilities

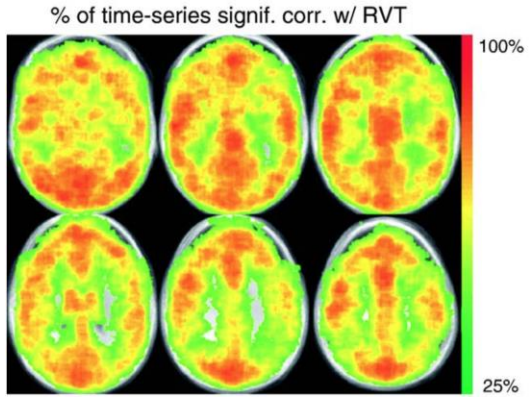
Participant

Head Motion

Cardiac Function
Respiratory Function
Systemic Vascular Waves

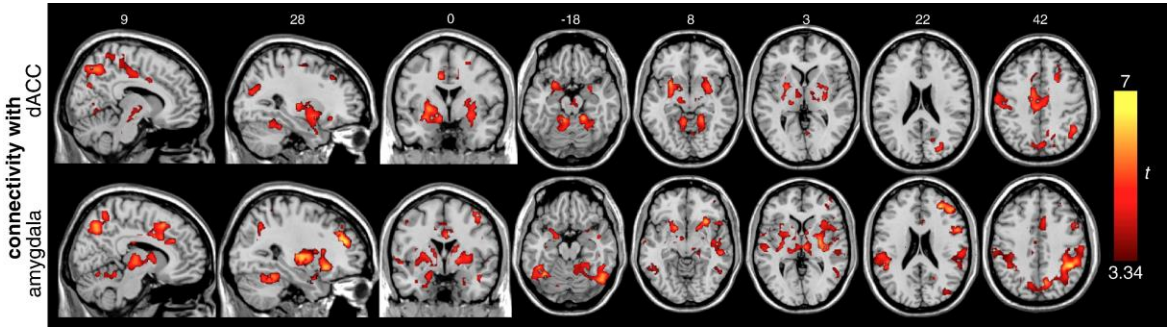
Respiratory Variation Effects





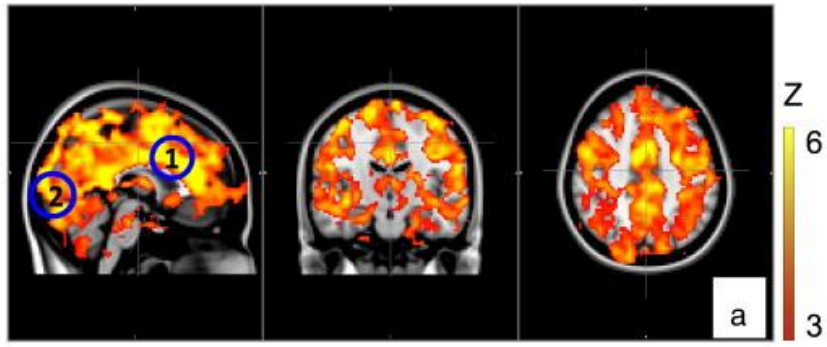
Birn et al. "Separating respiratory-variation-related fluctuations from neural-activity-related fluctuations in fMRI" NeuroImage (2006)

Heart Rate Variability



Chang et al. "Association between heart rate variability and fluctuations in resting-state functional connectivity" NeuroImage (2013)

Systemic Vascular Waves



Tong et al. "Evaluating the effects of systemic low frequency oscillations measured in the periphery on the ICA results of resting state networks" NeuroImage (2013)

How to estimate functional connectivity: pay special attention to confounds with spatial structure

Hardware

Slow Drifts, Thermal Noise, Coil Instabilities

Participant

Head Motion

Cardiac Function
Respiratory Function
Systemic Vascular Waves

Acquire concurrent physiological recordings

How to estimate functional connectivity: pay special attention to confounds with spatial structure

Hardware

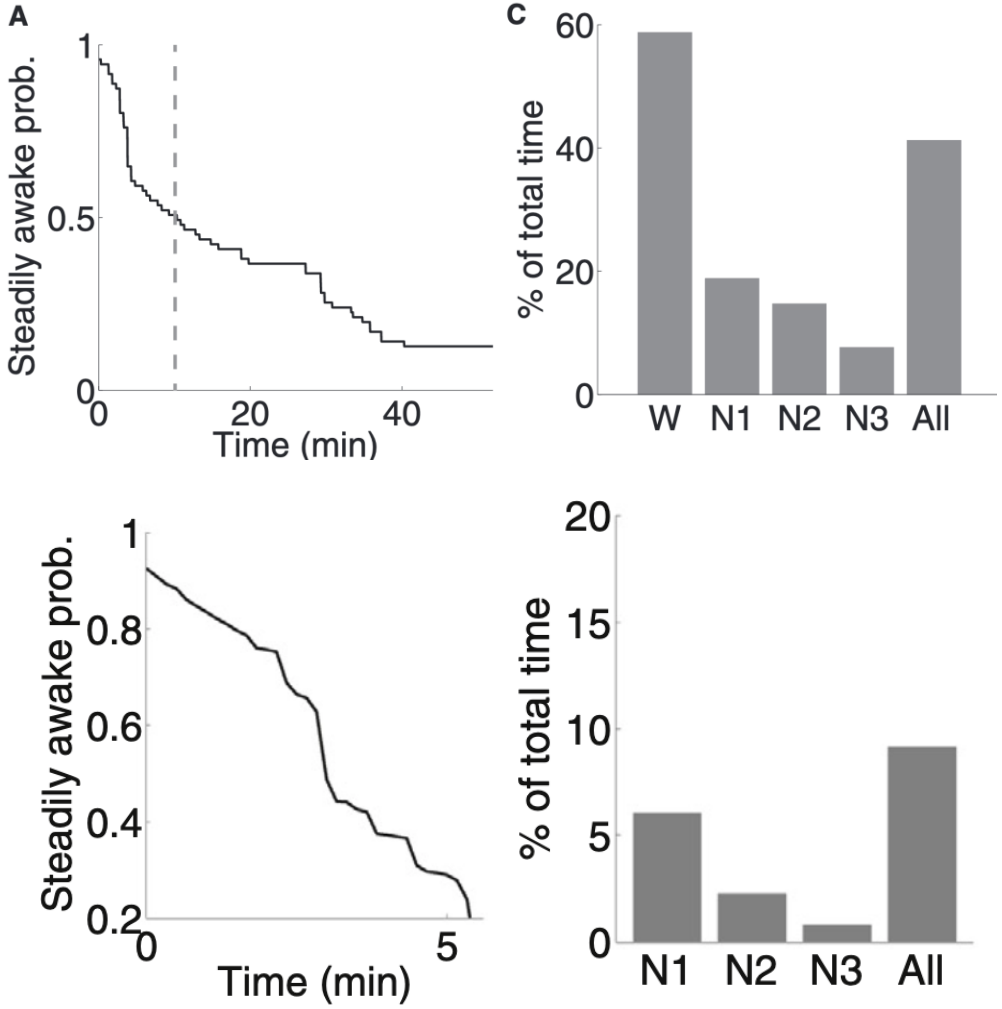
Slow Drifts, Thermal Noise, Coil Instabilities

Participant

Head Motion

Cardiac Function
Respiratory Function
Systemic Vascular Waves

Arousal/Wakefulness
Time of Day, Seasonality
Acclimation to Scanner
Caffeine
Spontaneous Thoughts, …



Tagliazucchi et al. Neuron (2014)

How to estimate functional connectivity: pay special attention to confounds with spatial structure

Hardware

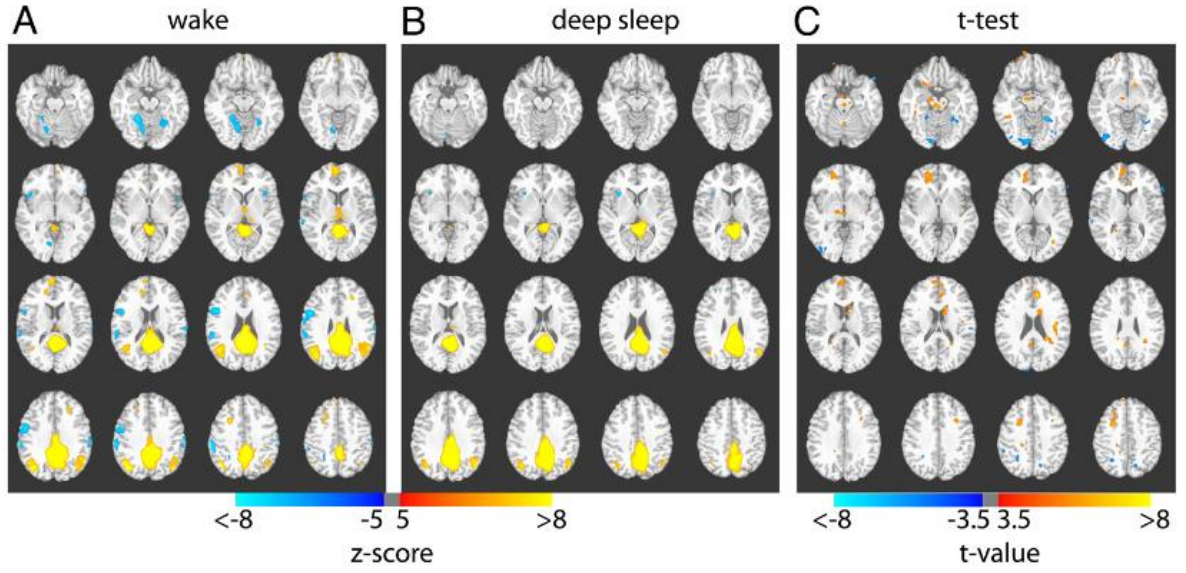
Slow Drifts, Thermal Noise, Coil Instabilities

Participant

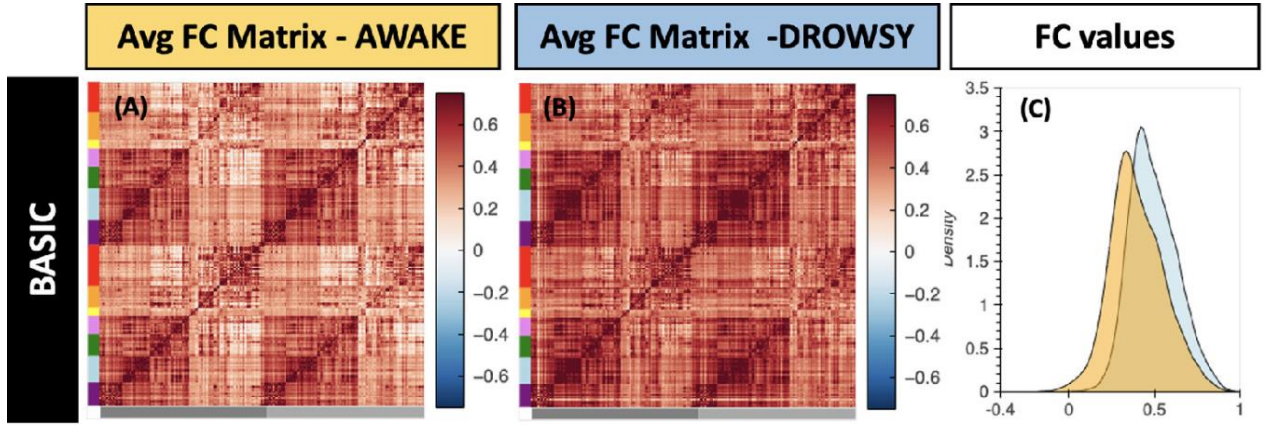
Head Motion

Cardiac Function
Respiratory Function
Systemic Vascular Waves

Arousal/Wakefulness
Time of Day, Seasonality
Acclimation to Scanner
Caffeine
Spontaneous Thoughts, …



Horovitz et al. PNAS (2009)



Gonzalez-Castillo et al. NeuroImage (2022)

How to estimate functional connectivity: pay special attention to confounds with spatial structure

Hardware

Slow Drifts, Thermal Noise, Coil Instabilities

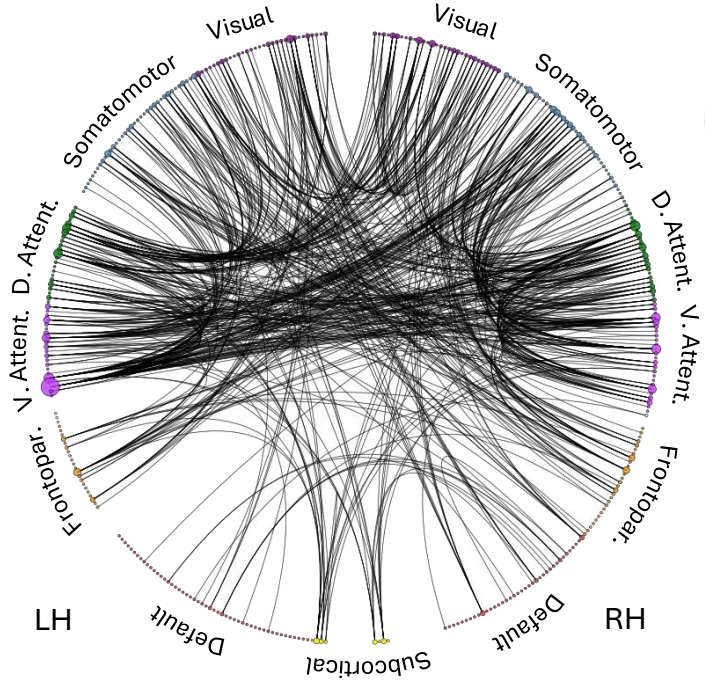
Participant

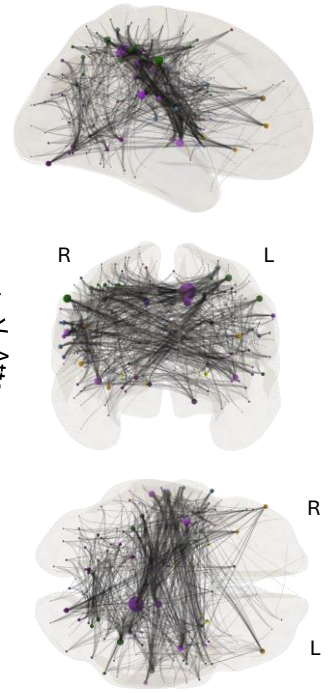
Head Motion

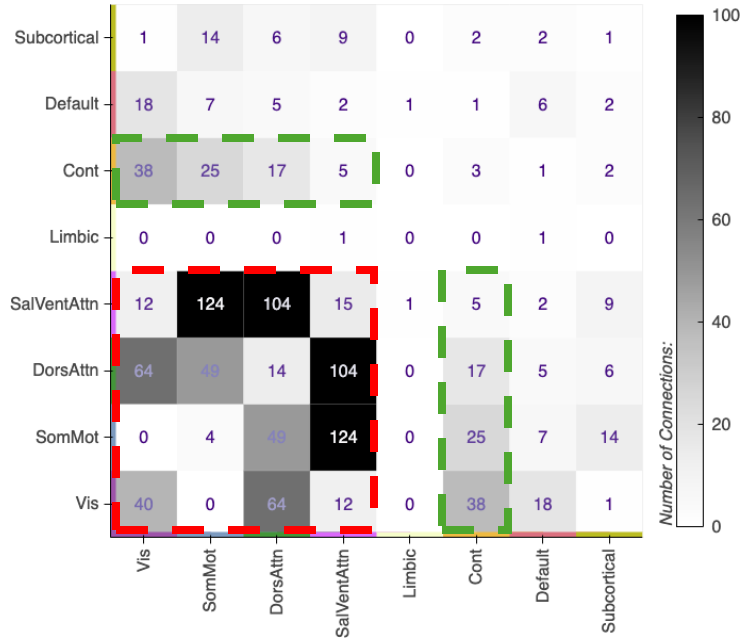
Cardiac Function
Respiratory Function
Systemic Vascular Waves

Arousal/Wakefulness
Time of Day, Seasonality
Acclimation to Scanner
Caffeine
Spontaneous Thoughts, ...

Network-Level (p_{FWE}<0.05) Differences in Functional Connectivity across sets [Surr-Neg-Self > Images-Pos-Others]







Gonzalez-Castillo et al. “In-scanner thoughts shape resting-state functional connectivity: particpants’ resting thoughts matter” BioRxiv (2024) / Under Review

Learning Objectives

Define Functional Connectivity

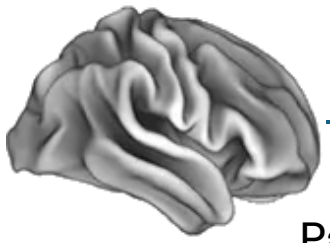
How to estimate Functional Connectivity

Static vs. Dynamic Functional Connectivity

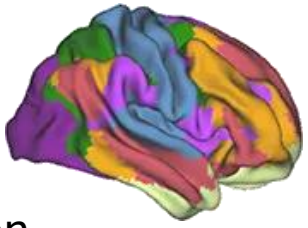
How to estimate Dynamic Functional Connectivity

Special Considerations for task-based studies

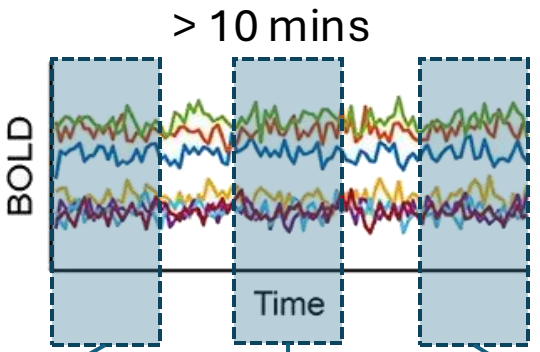
Static vs. Dynamic Functional Connectivity



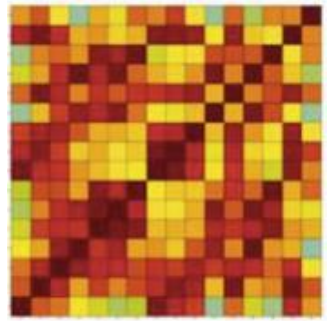
Choose Parcellation



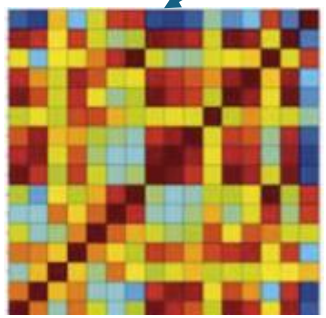
Extract Timeseries

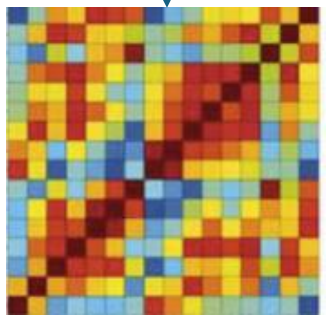


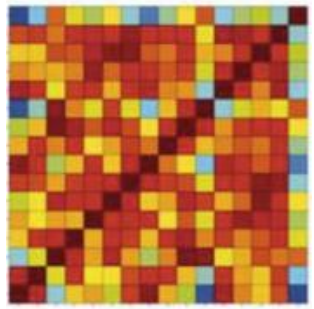
Compute Pair-wise Correlation



Static FC







300 - 360s

540 - 600s

Time-varying FC

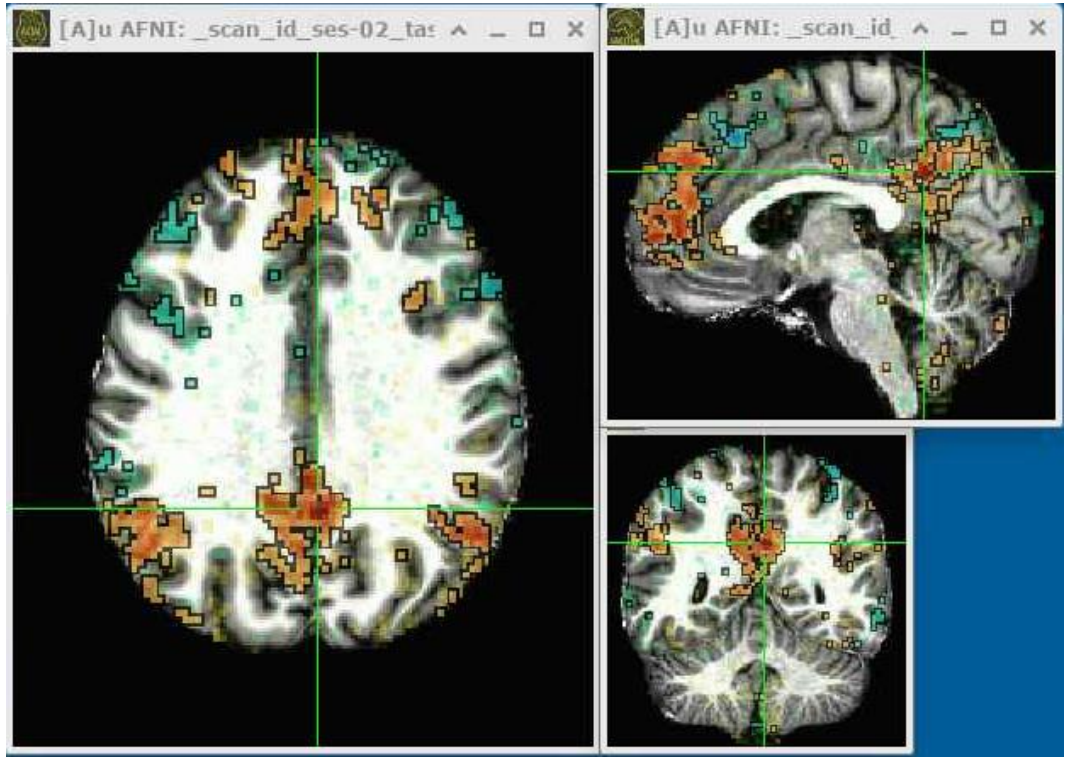
February 01 2020

Questions and controversies in the study of time-varying functional connectivity in resting fMRI

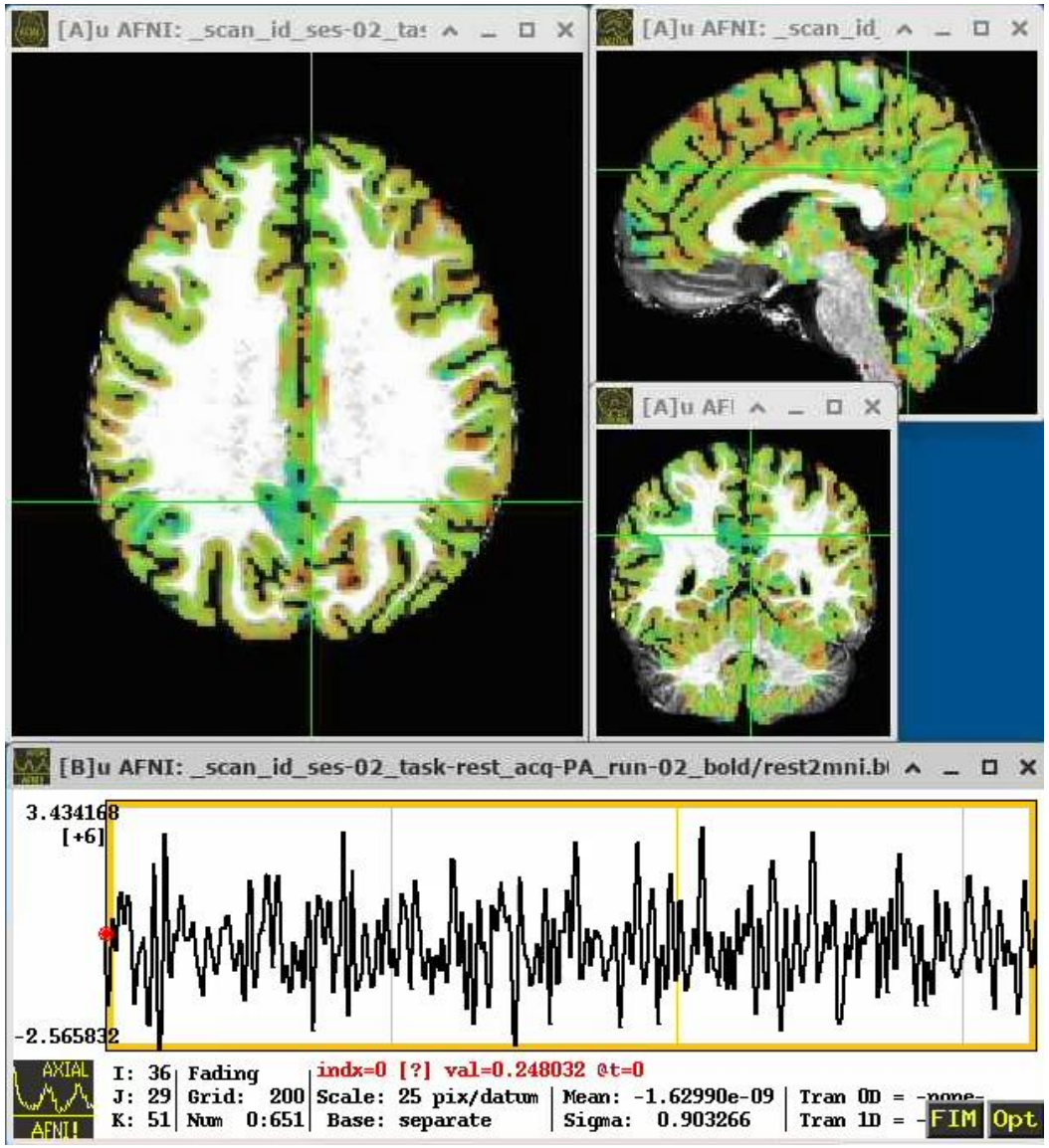
In Special Collection: CogNet

Daniel J. Lurie, Daniel Kessler, Danielle S. Bassett, Richard F. Betzel, Michael Breakspear, Shella Kheilholz, Aaron Kucyi, Raphaël Liégeois, Martin A. Lindquist, Anthony Randal McIntosh, Russell A. Poldrack, James M. Shine, William Hedley Thompson, Natalia Z. Bielczyk, Linda Douw, Dominik Kraft, Robyn L. Miller, Muthuraman Muthuraman, Lorenzo Pasquini, Adeel Razi, Diego Vidaurre, Hua Xie, Vince D. Calhoun

Static vs. Time-varying Functional Connectivity



Static FC for PCC Seed



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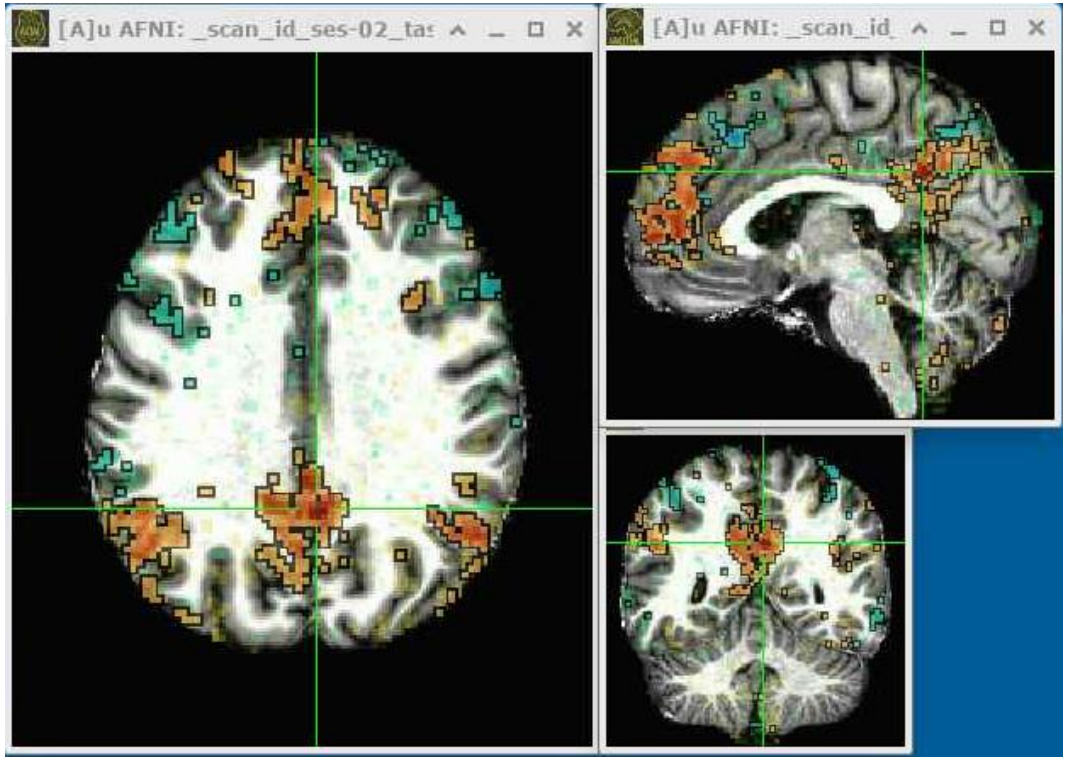
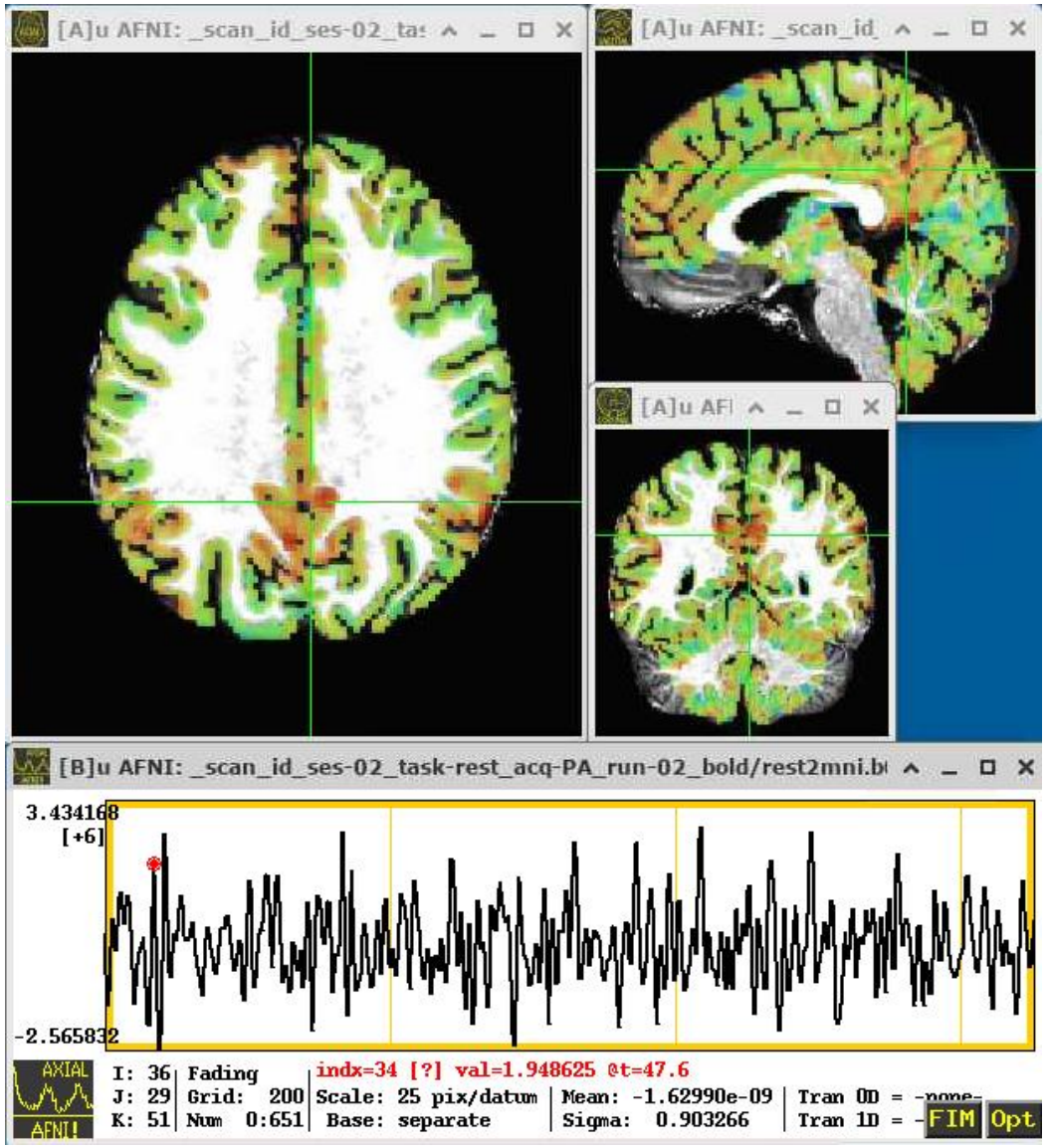


Static FC for PCC Seed



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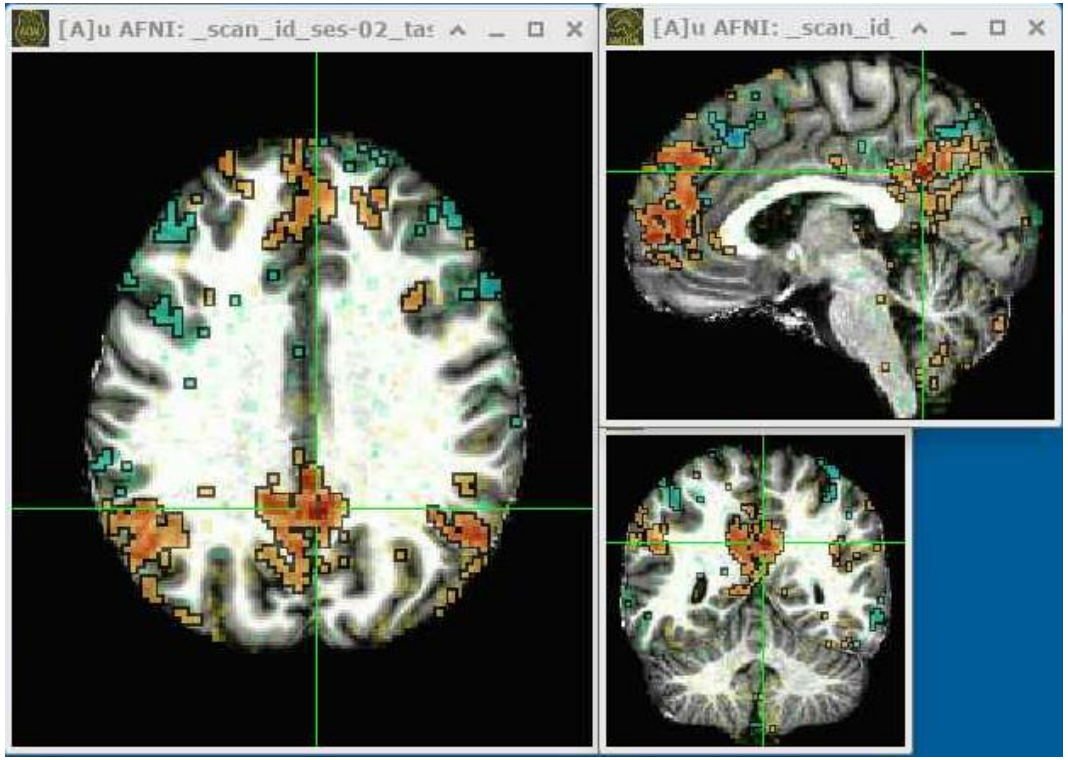

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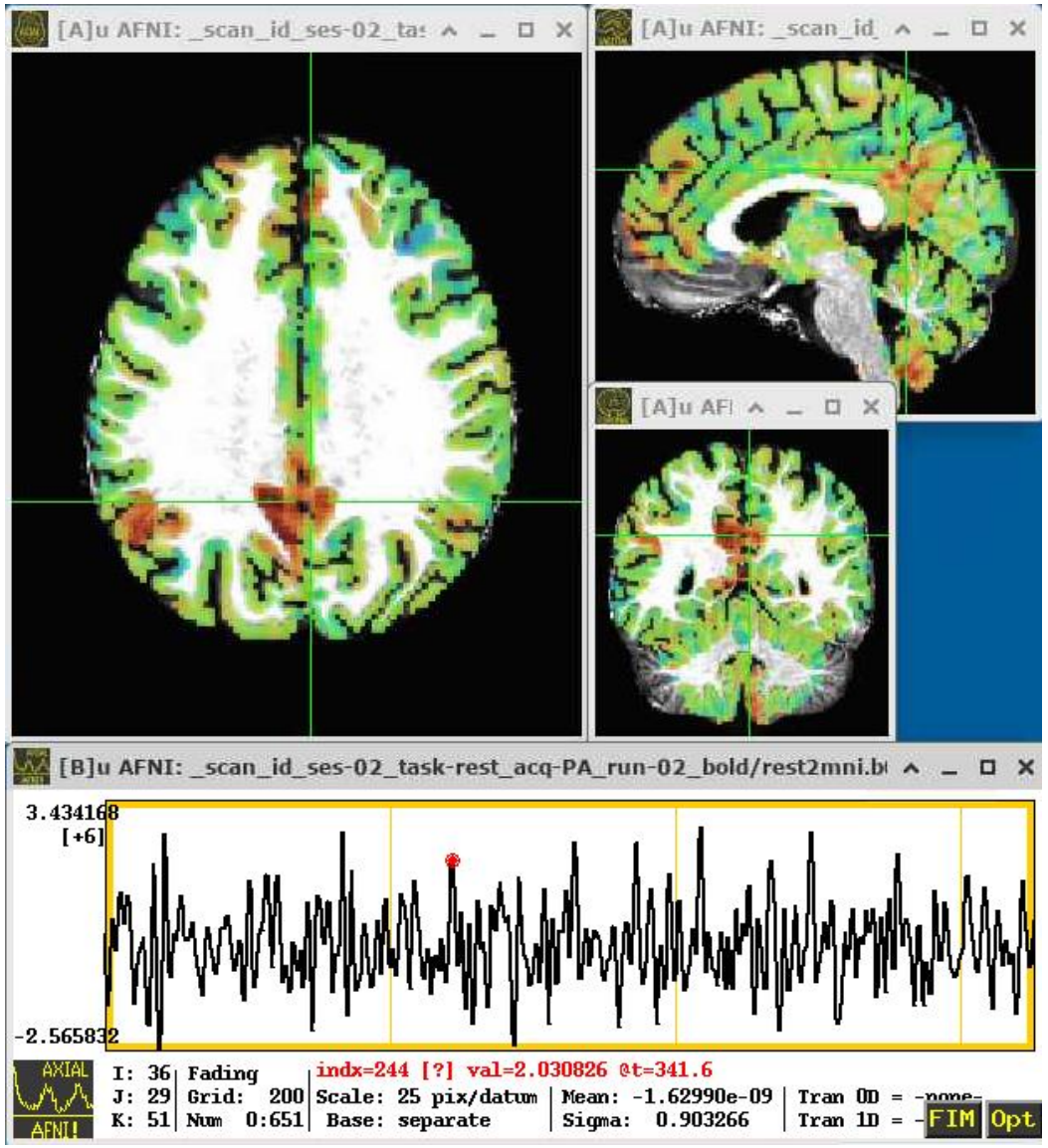
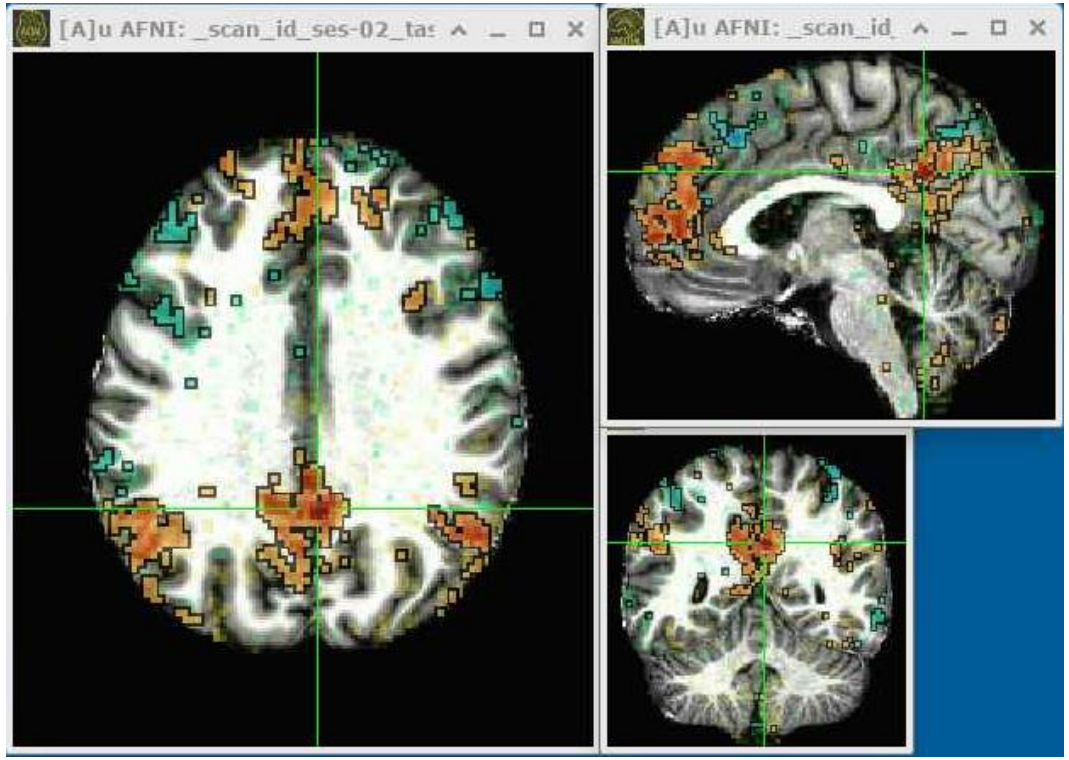


Static vs. Time-varying Functional Connectivity



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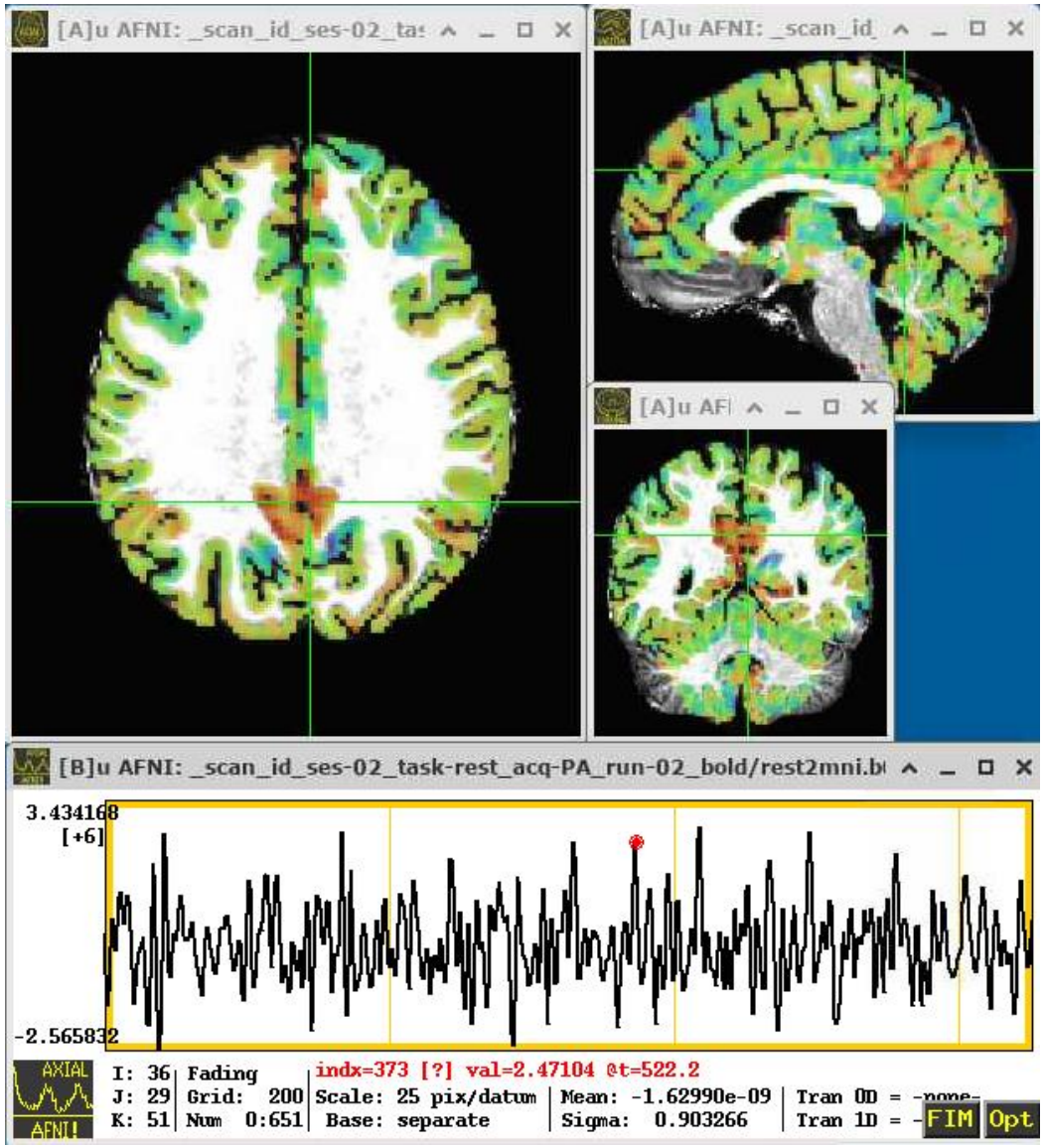

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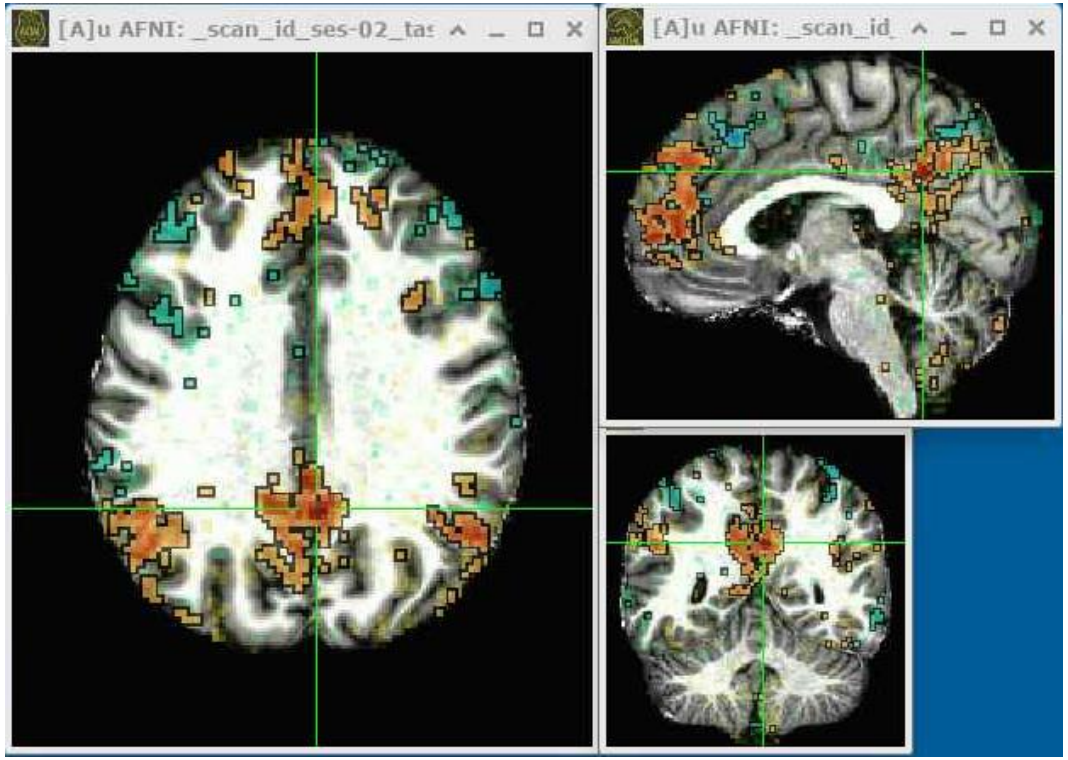
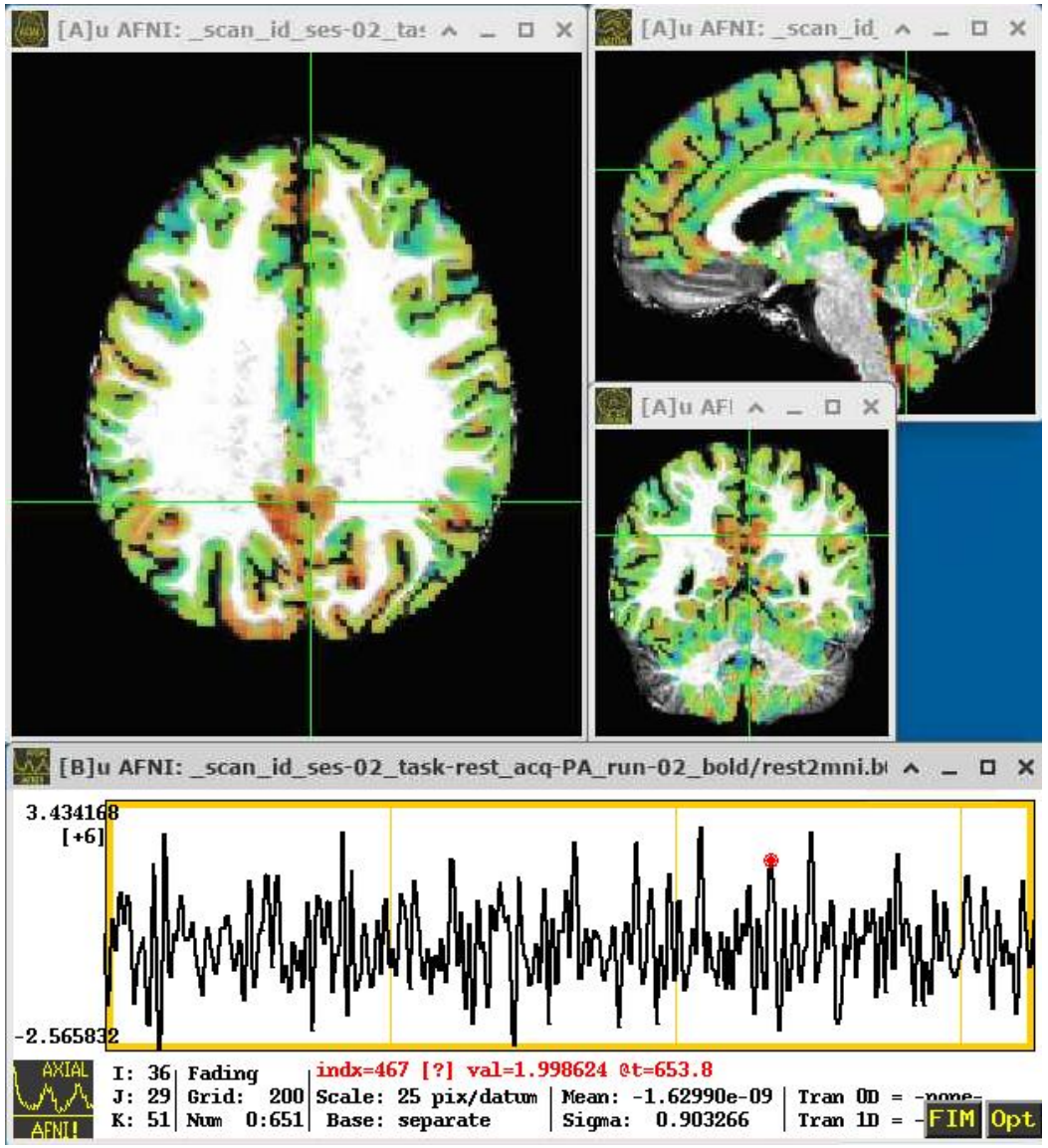


Static FC for PCC Seed



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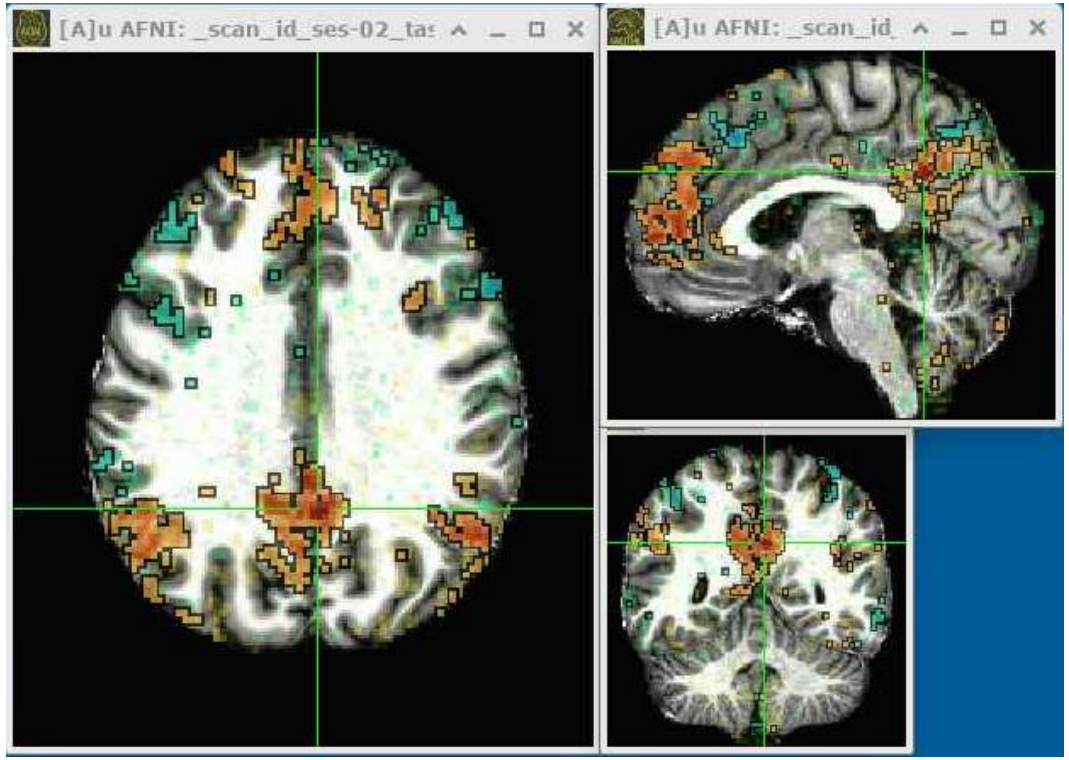

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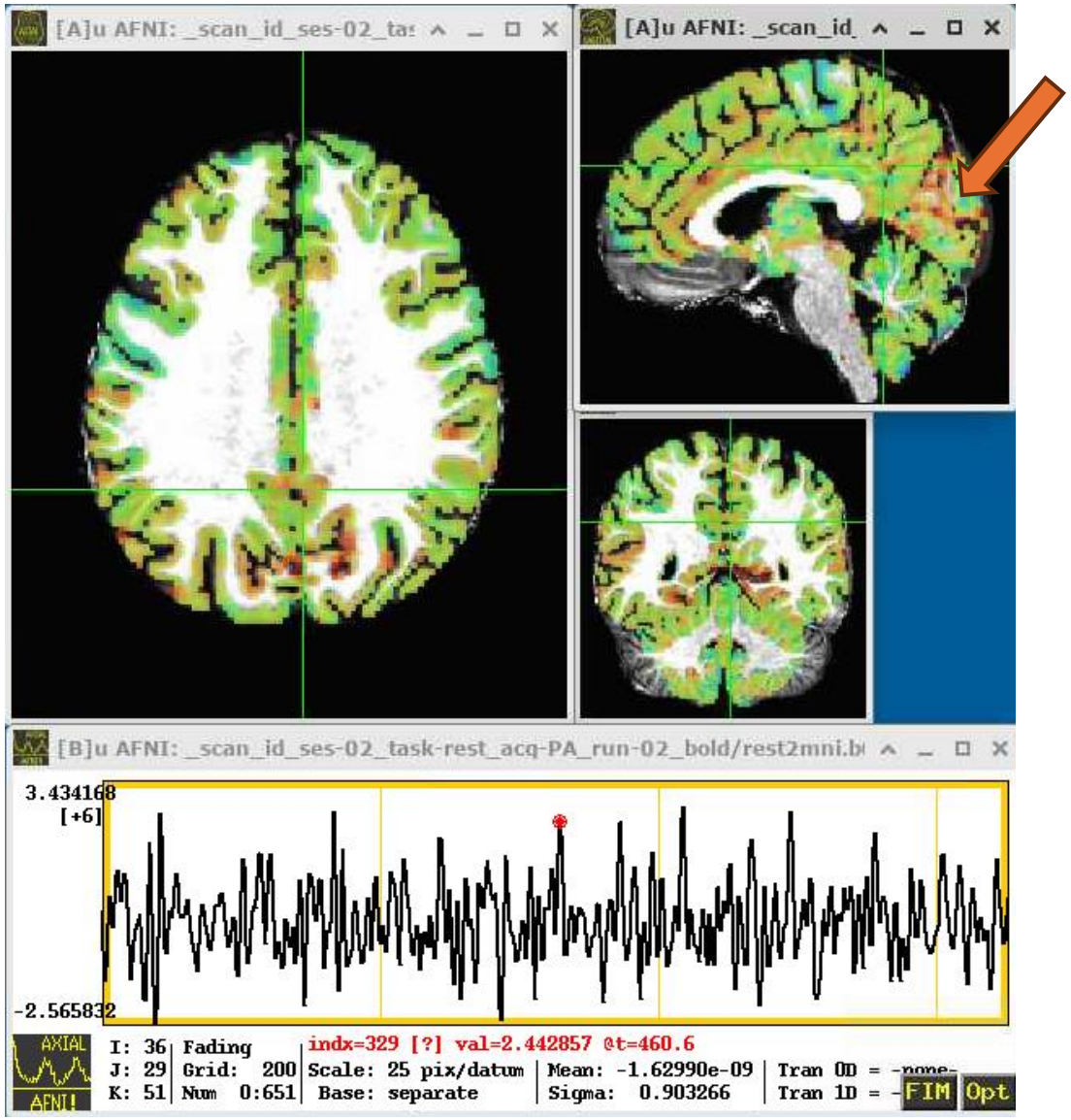

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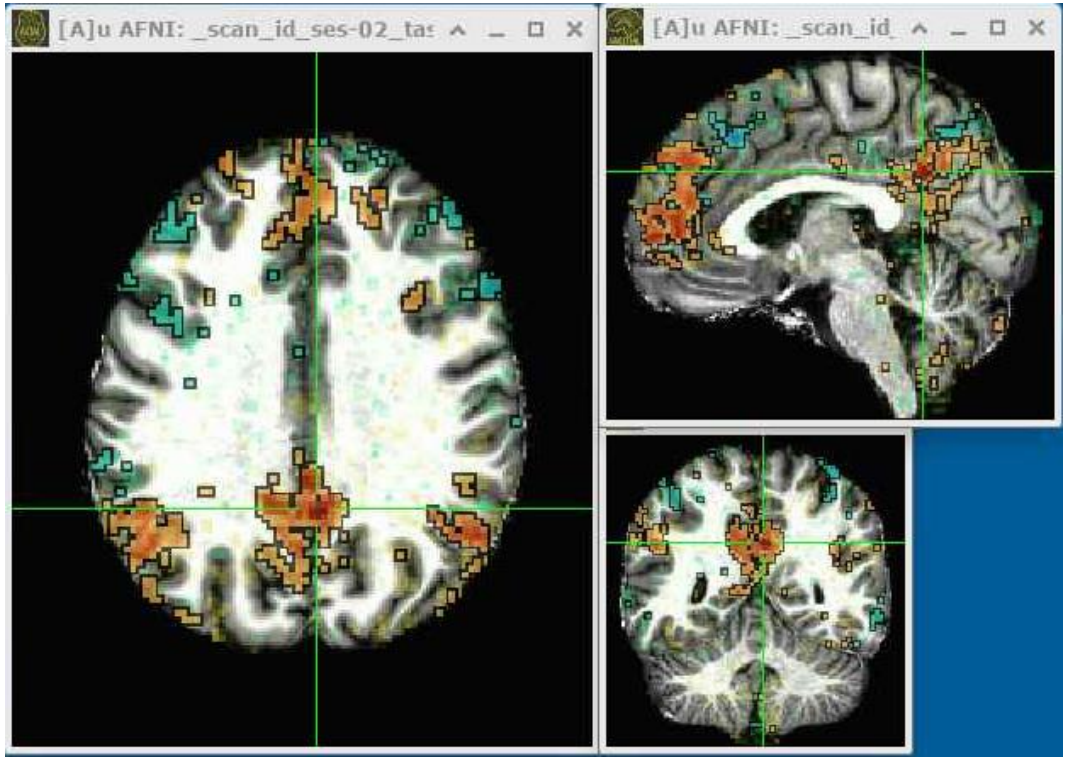

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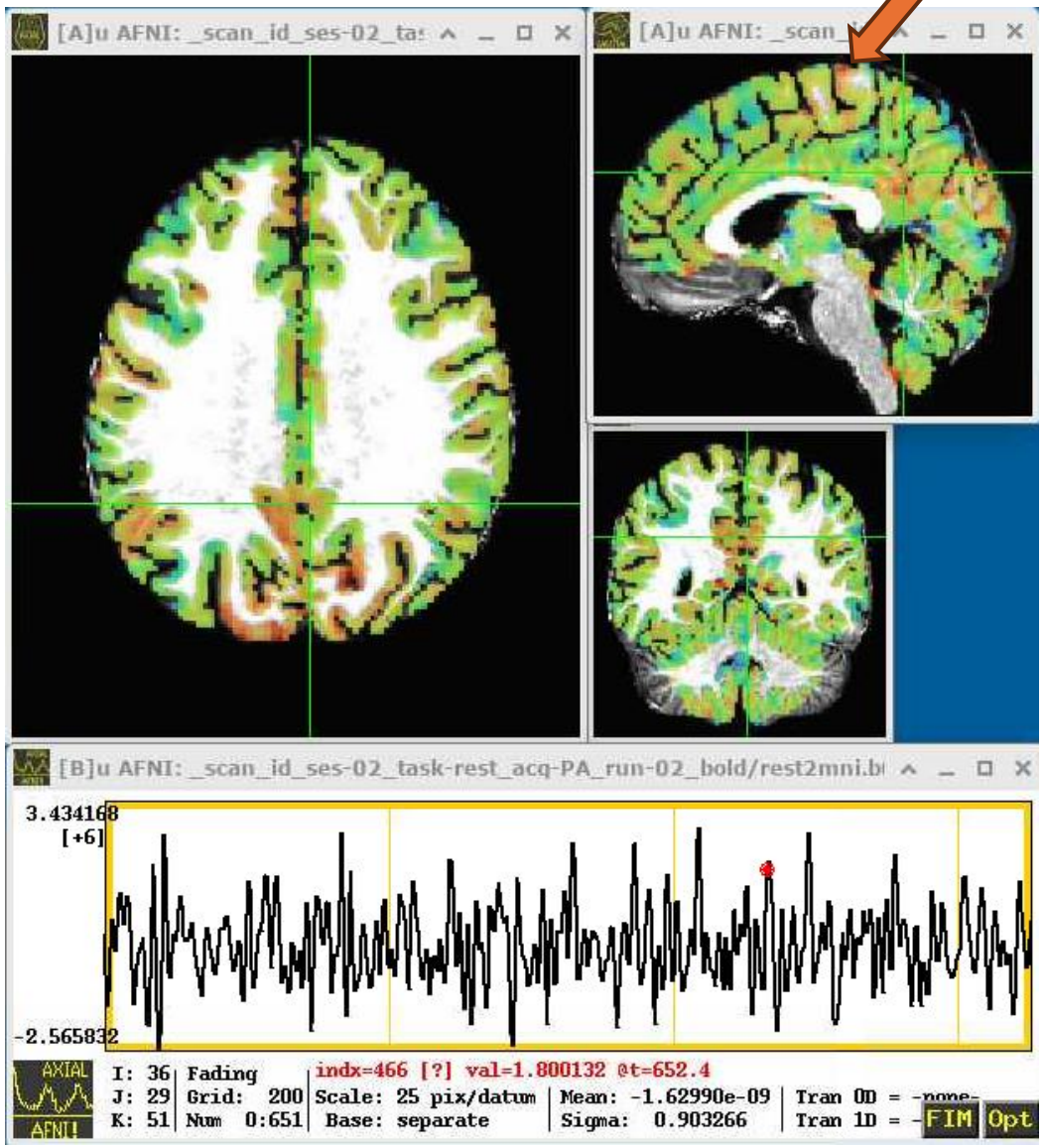
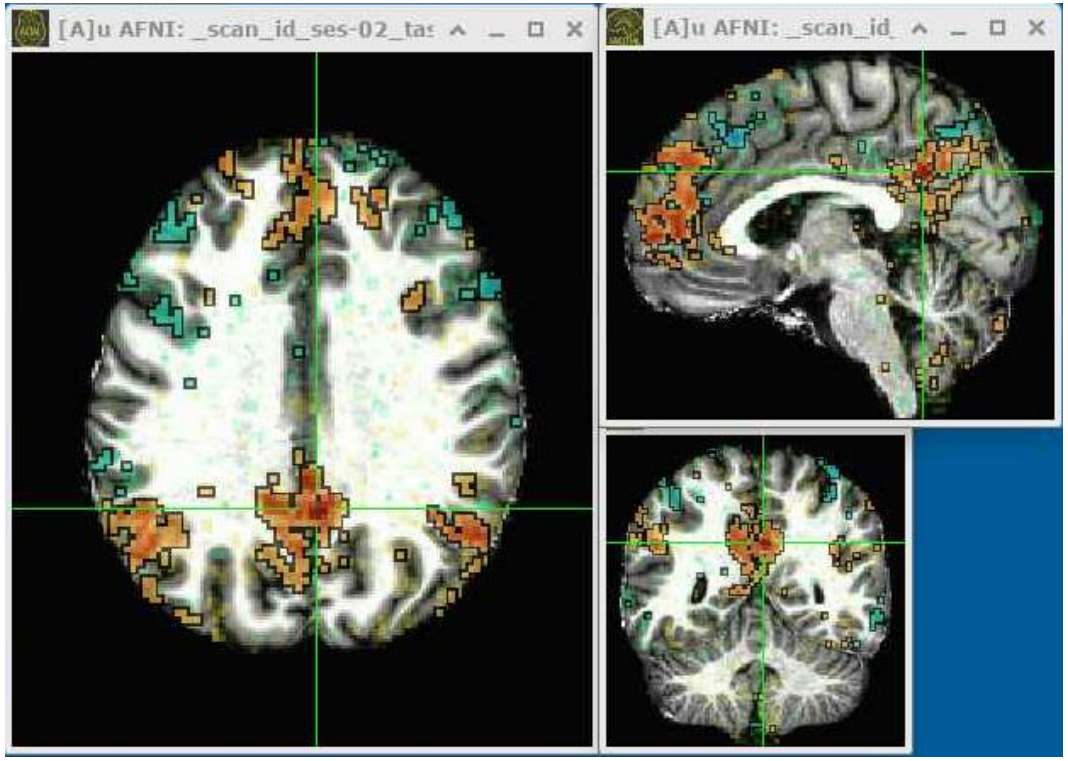
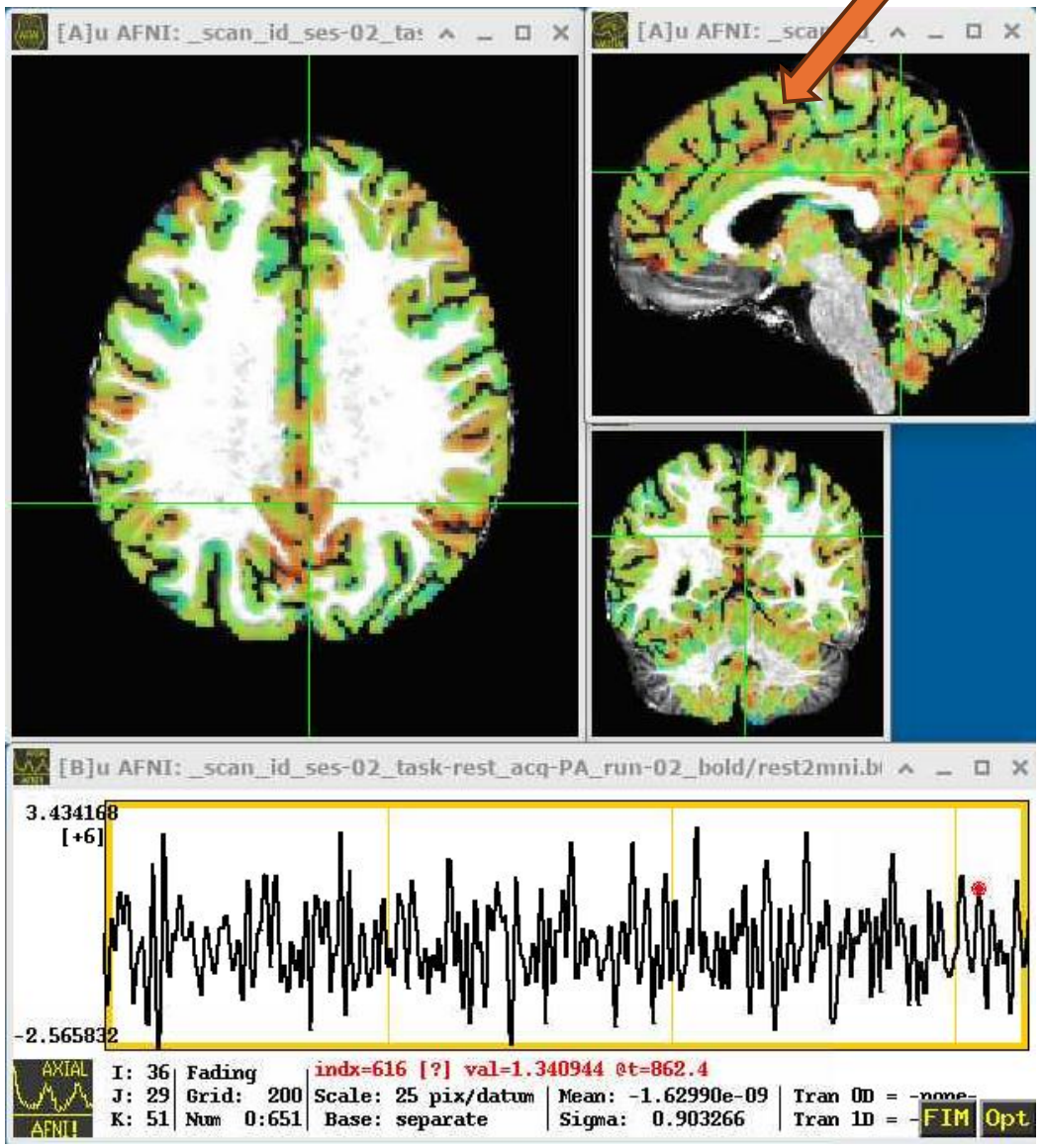


Static vs. Time-varying Functional Connectivity



Static FC for PCC Seed



Learning Objectives

Define Functional Connectivity

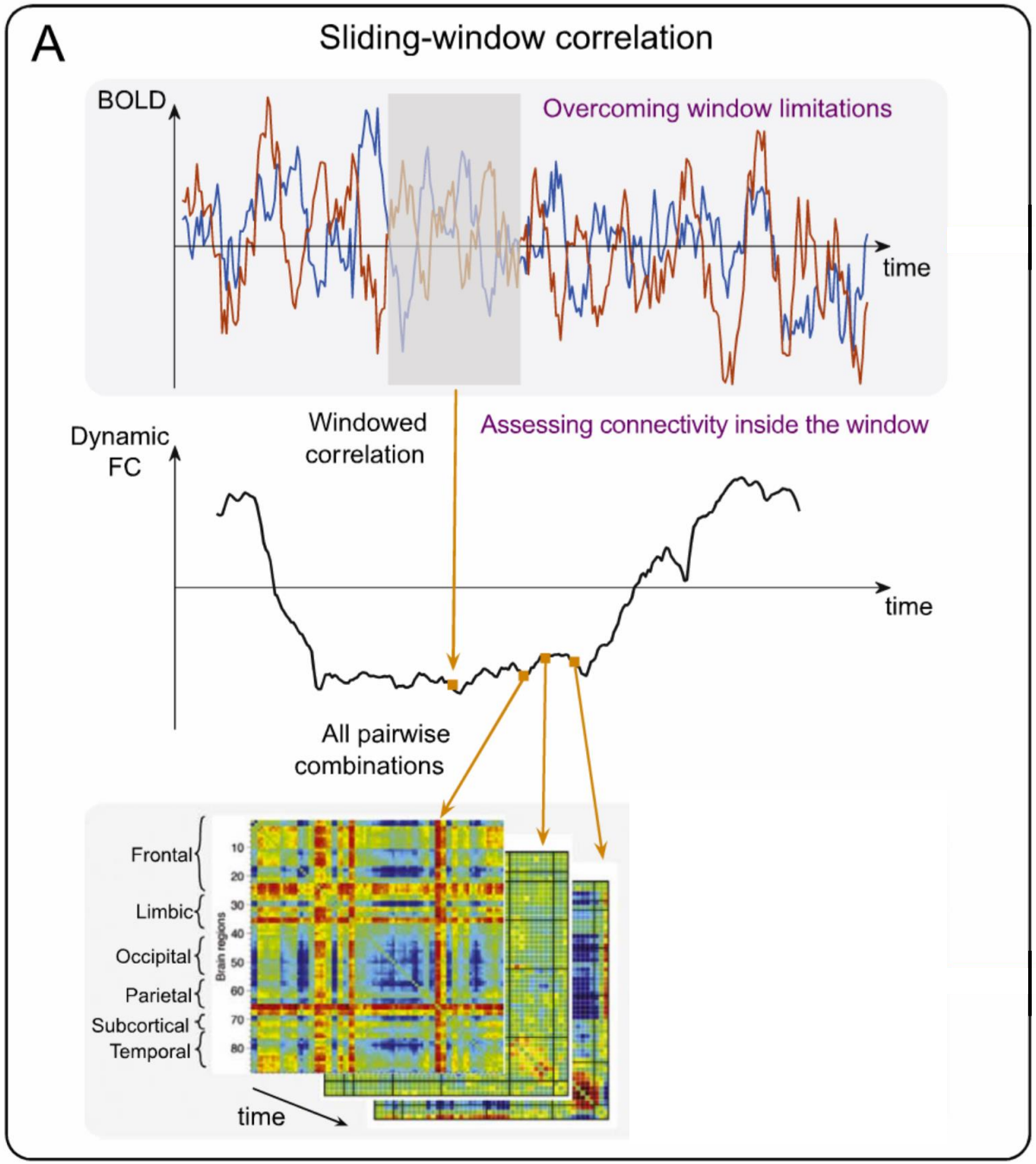
How to estimate Functional Connectivity

Static vs. Dynamic Functional Connectivity

How to estimate Dynamic Functional Connectivity

Special Considerations for task-based studies

How to estimate Time-varying FC



ELSEVIER

NeuroImage

Volume 133, June 2016, Pages 111-128

Evaluation of sliding window correlation performance for characterizing dynamic functional connectivity and brain states

Sadia Shakil [a 1], Chin-Hui Lee [a 1], Shella Dawn Keilholz [b c 2]

ELSEVIER

NeuroImage

Volume 104, 1 January 2015, Pages 430-436

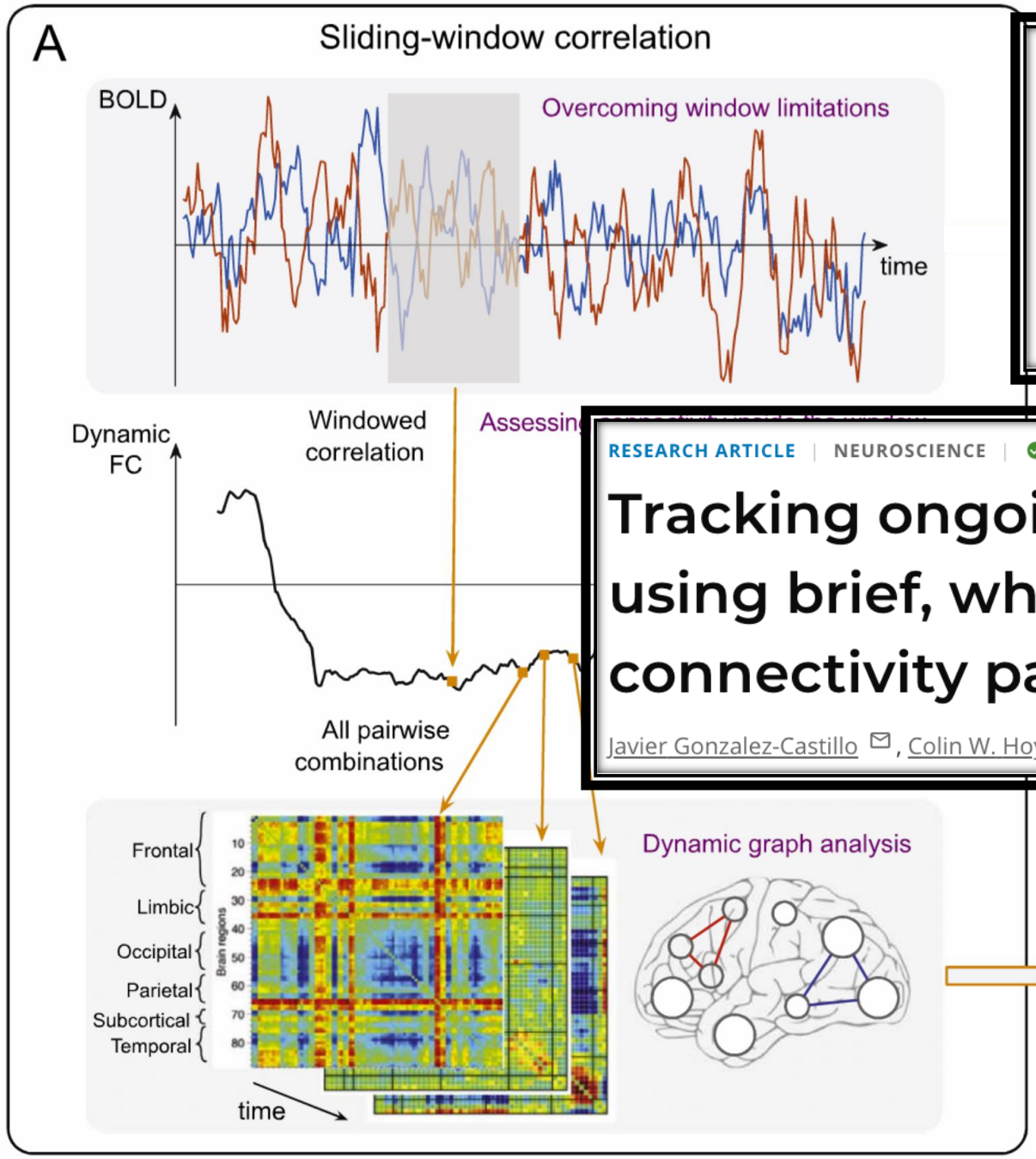
Comments and Controversies

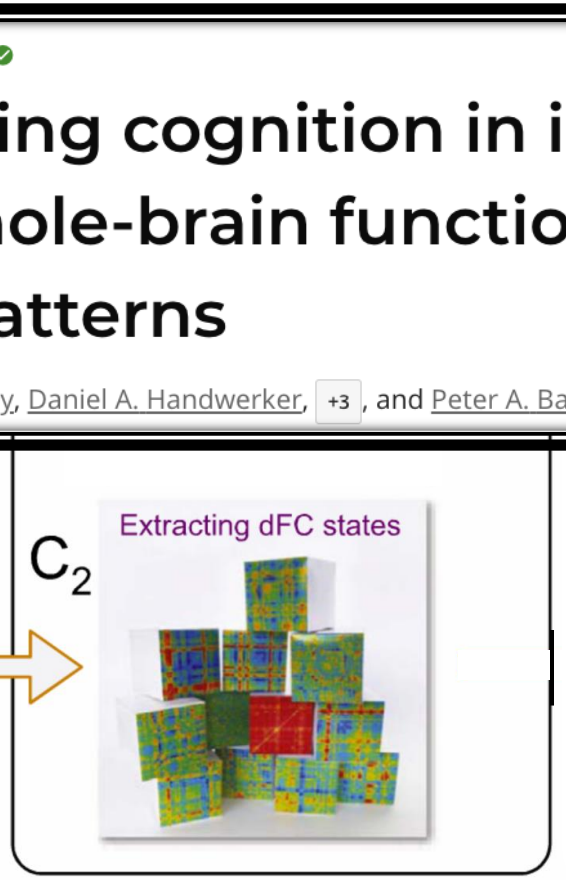
On spurious and real fluctuations of dynamic functional connectivity during rest

Nora Leonardi, Dimitri Van De Ville

Preti et al. (2016) NeuroImage

How to estimate Time-varying FC





JOURNAL ARTICLE

Tracking Whole-Brain Connectivity Dynamics in the Resting State

FREE

Elena A. Allen, Eswar Damaraju, Sergey M. Plis, Erik B. Erhardt, Tom Eichele, Vince D. Calhoun

Cerebral Cortex, Volume 24, Issue 3, March 2014, Pages 663–676,
https://doi.org/10.1093/cercor/bhs352
Published: 11 November 2012

RESEARCH ARTICLE | NEUROSCIENCE

Tracking ongoing cognition in individuals using brief, whole-brain functional connectivity patterns

Javier Gonzalez-Castillo, Colin W. Hoy, Daniel A. Handwerker, +3, and Peter A. Bandettini Authors Info & Affiliations

Preti et al. (2016) NeuroImage

How to estimate Time-varying FC

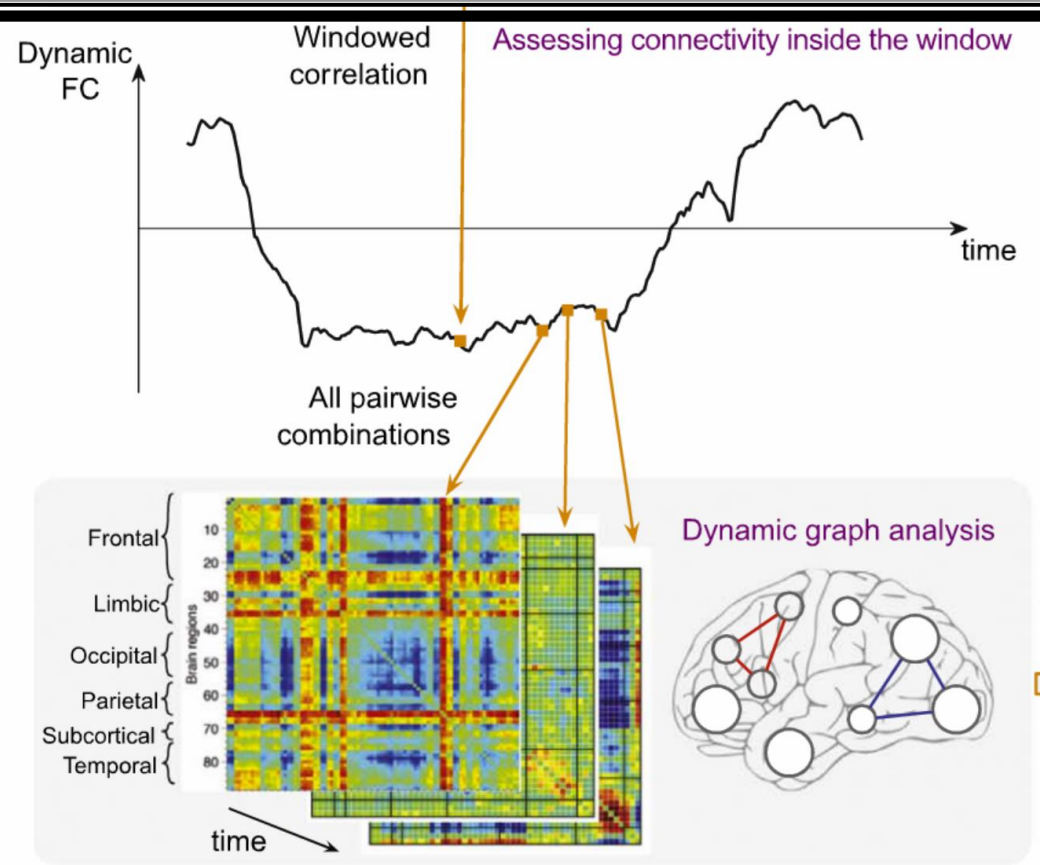
A

Sliding-window correlation

Criticality in large-scale brain fMRI dynamics unveiled by a novel point process analysis

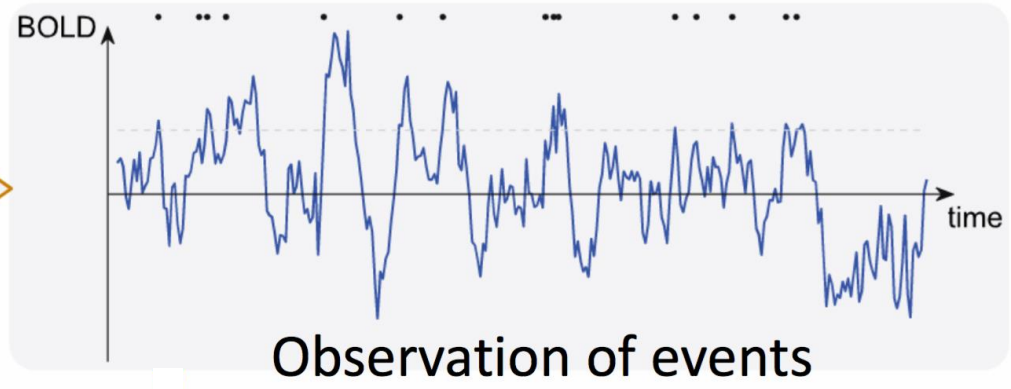
Enzo Tagliazucchi[1,2] Pablo Balenzuela[1,3] Daniel Fraiman[3,4] Dante R. Chialvo[3,5,6]*

1 Departamento de Física, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina
2 Department of Neurology and Brain Imaging Center, Goethe-University Frankfurt, Frankfurt am Main, Germany
3 Consejo Nacional de Investigaciones Científicas y Tecnológicas, Buenos Aires, Argentina
4 Departamento de Matemática y Ciencias, Universidad de San Andrés, Buenos Aires, Argentina
5 Facultad de Ciencias Médicas, Universidad Nacional de Rosario, Rosario, Argentina
6 David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA



B

Frame-wise analysis



Observation of events

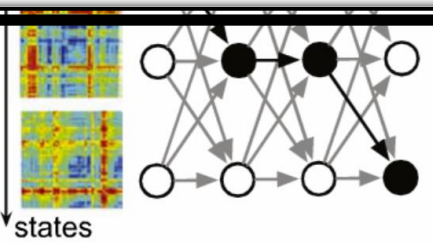
ELSEVIER

NeuroImage

Volume 202, 15 November 2019, 116081

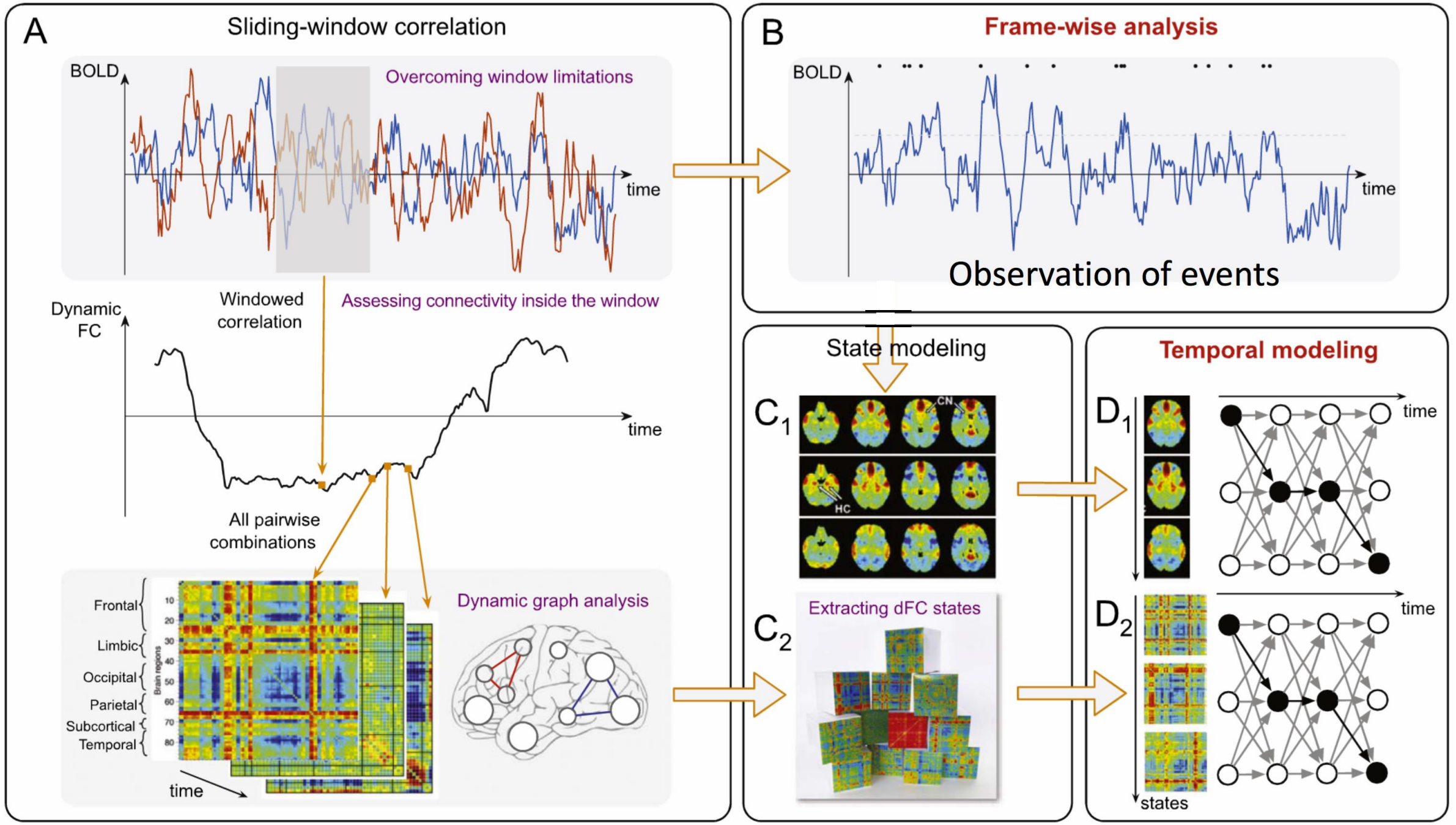
A deconvolution algorithm for multi-echo functional MRI: Multi-echo Sparse Paradigm Free Mapping

César Caballero-Gaudes [a 1], Stefano Moia [a], Puja Panwar [b], Peter A. Bandettini [b c], Javier Gonzalez-Castillo [b 1]



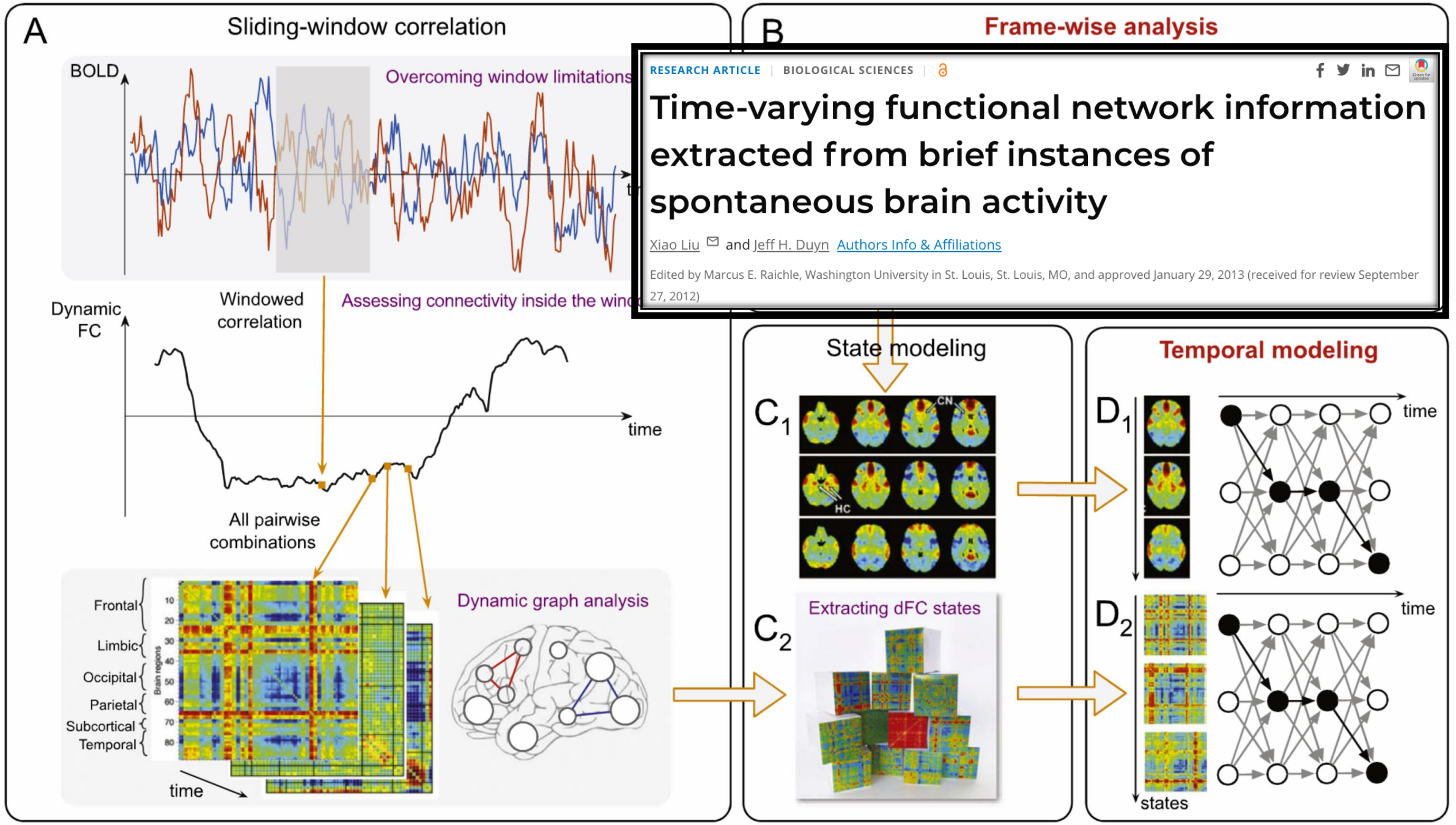
Preti et al. (2016) NeuroImage

How to estimate Time-varying FC



Preti et al. (2016) NeuroImage

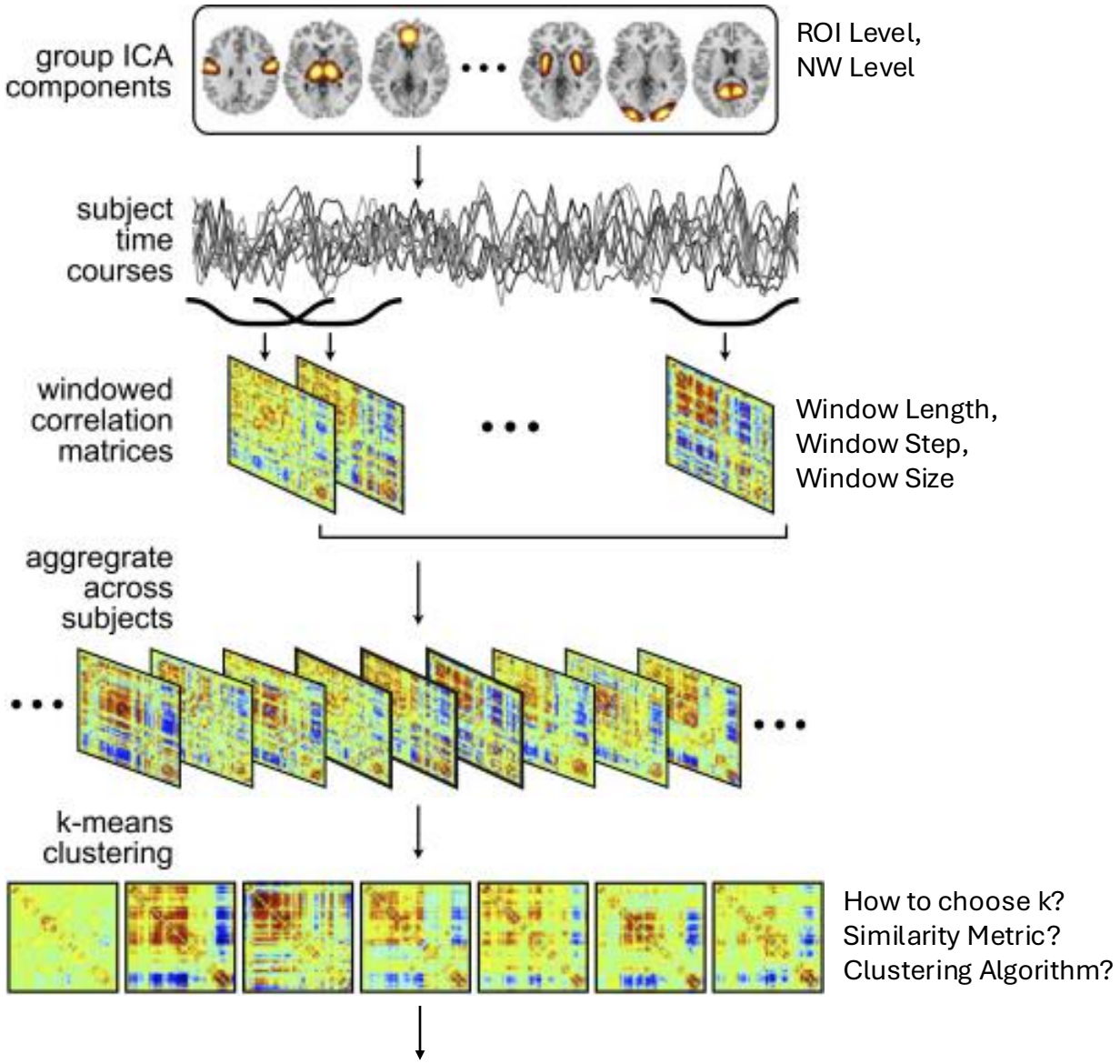
How to estimate Time-varying FC



Preti et al. (2016) NeuroImage

Example of State Modeling based on sliding window correlation

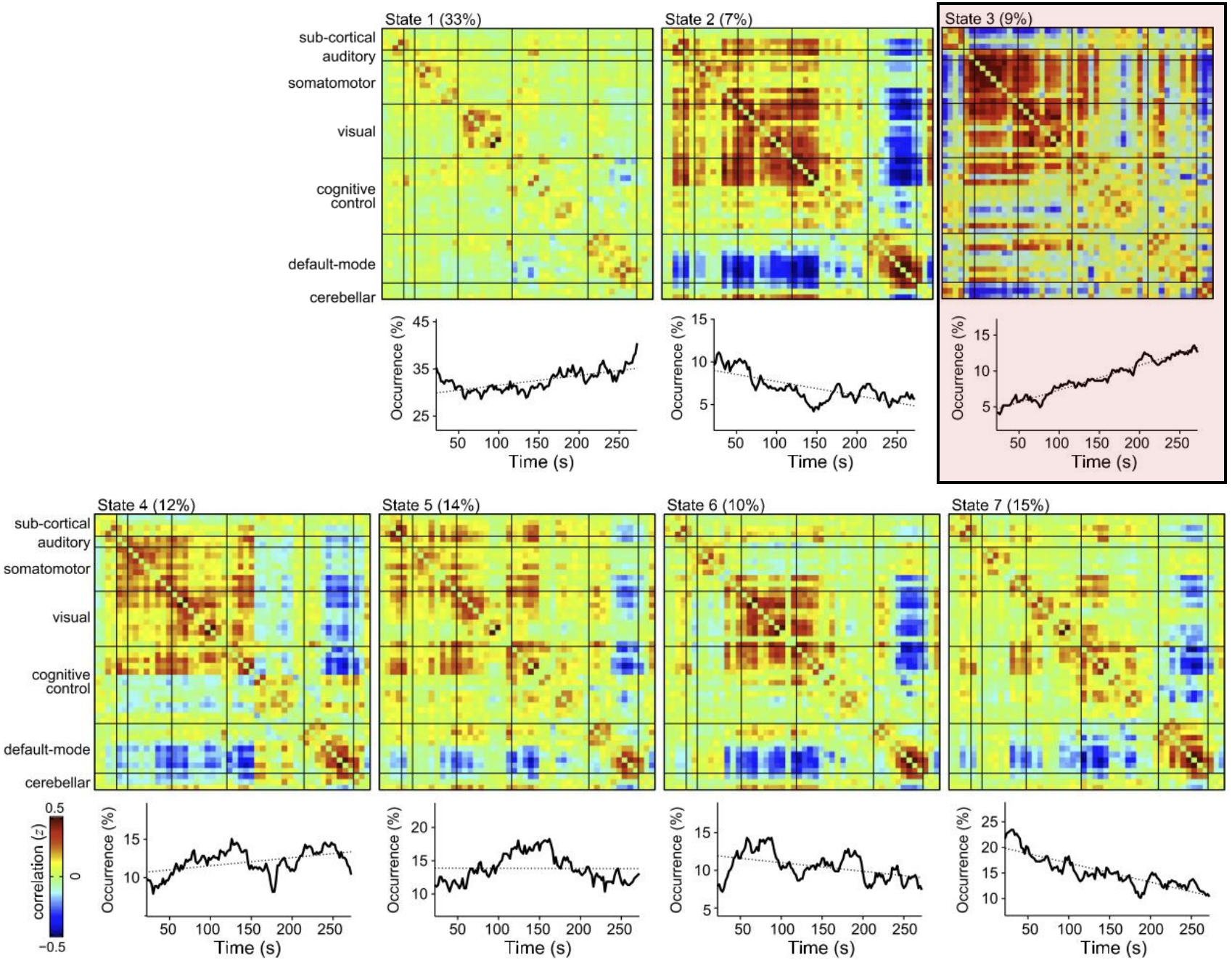
ASSUMPTION: FC Dynamics is appropriately modeled as a succession of a finite number of discrete FC configurations with sharp transitions between them.



Summary Statistics (e.g., dwell times, number of transitions, trajectories)

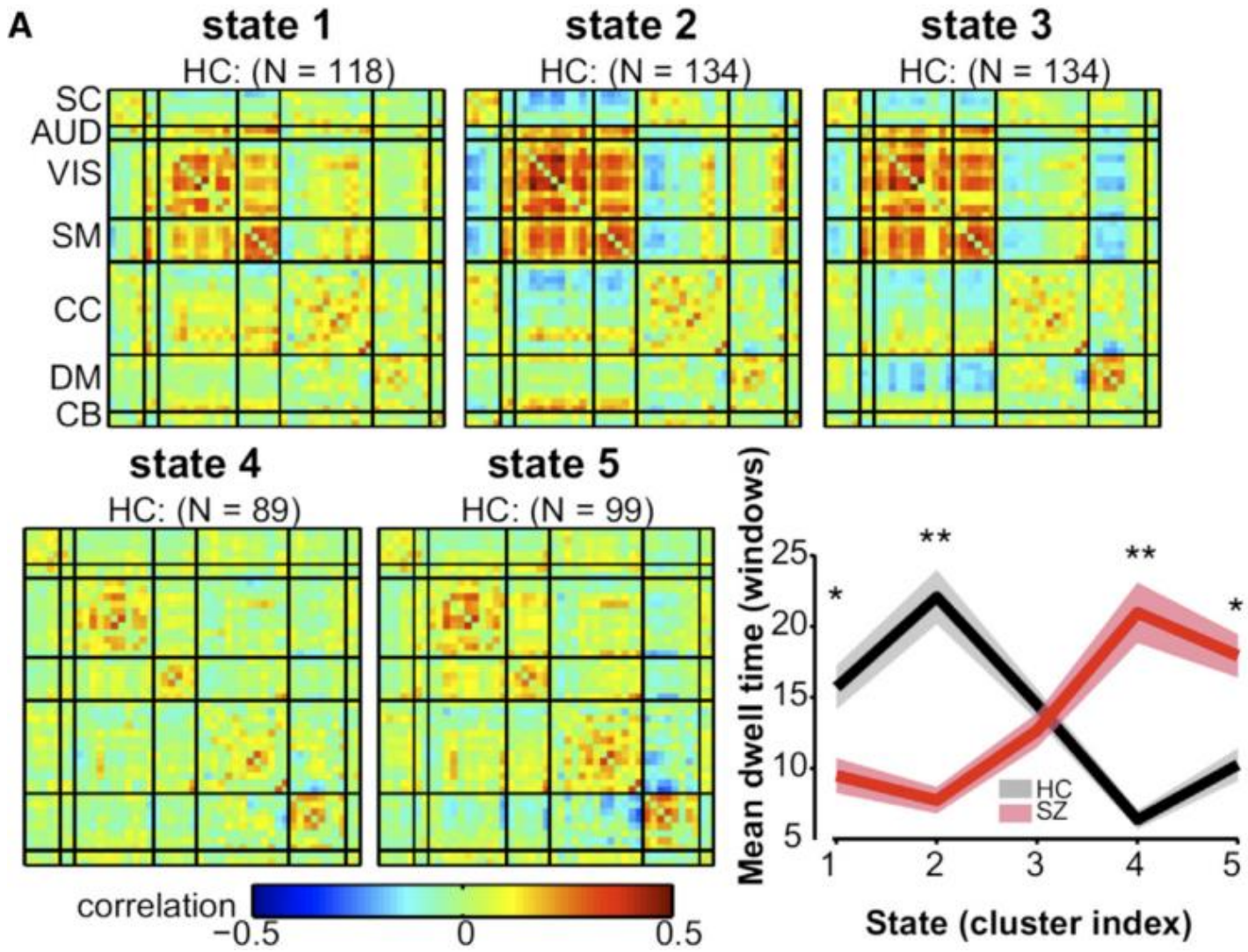
Allen et al. Cer. Cortex, 2014

Example of State Modeling based on sliding window correlation



Allen et al. Cer. Cortex, 2014

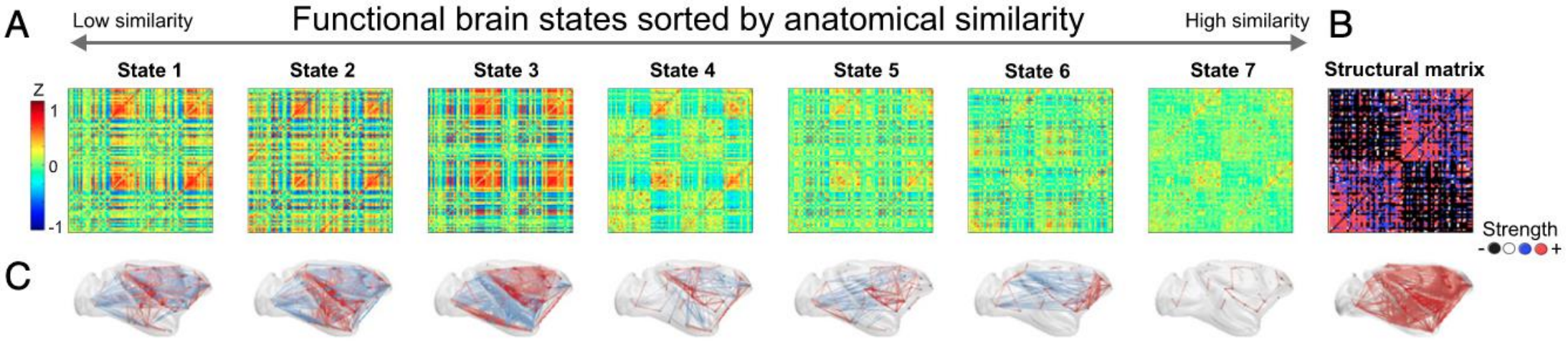
Example of State Modeling based on sliding window correlation (II)

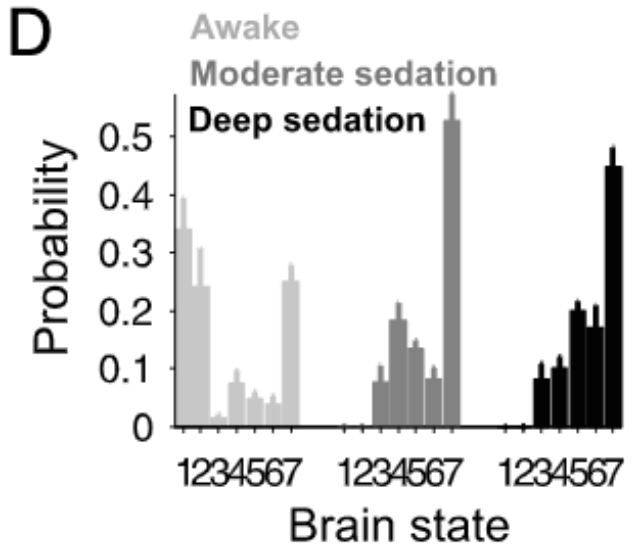


Dynamic states in a large (n > 300) data set of schizophrenia patients and controls in which the patients are spending significantly more time in the relatively less connected state 4.

Damaraju et al. NeuroImage Clinical, 2014

Dynamic FC is reduced as consciousness levels decrease

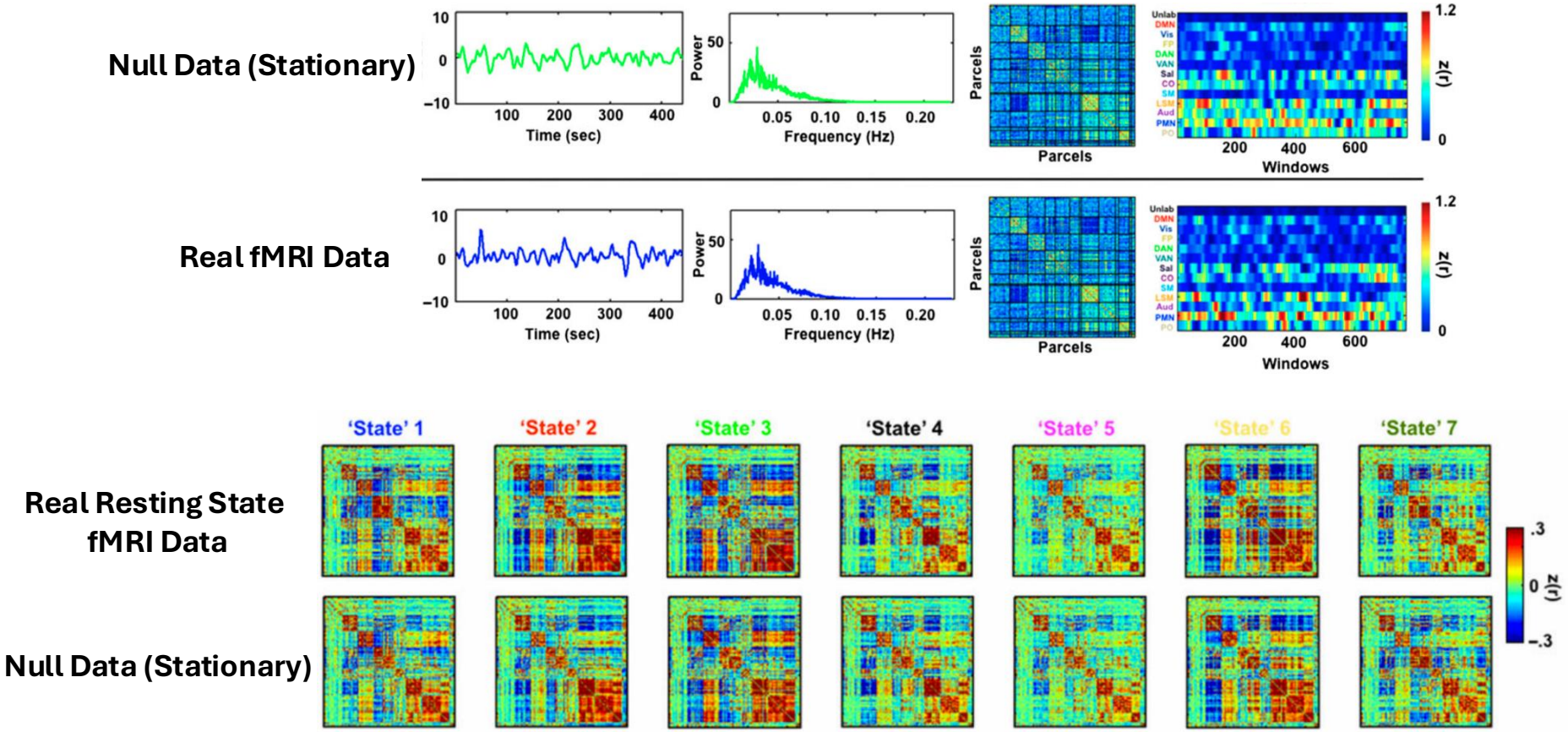




- "Under anesthesia, the more frequent functional connectivity patterns inherit the structure of anatomical connectivity, exhibit fewer small-world properties, and lack negative correlations"
- "Wakefulness is characterized by the sequential exploration of a richer repertoire of functional configurations, often dissimilar to anatomical structure, and comprising positive and negative correlations among brain regions"
- "Rich functional dynamics might constitute a signature of consciousness"

Barttfeld et al. PNAS (2015)

CONTROVERSY: Is it meaningful/neuronally driven?

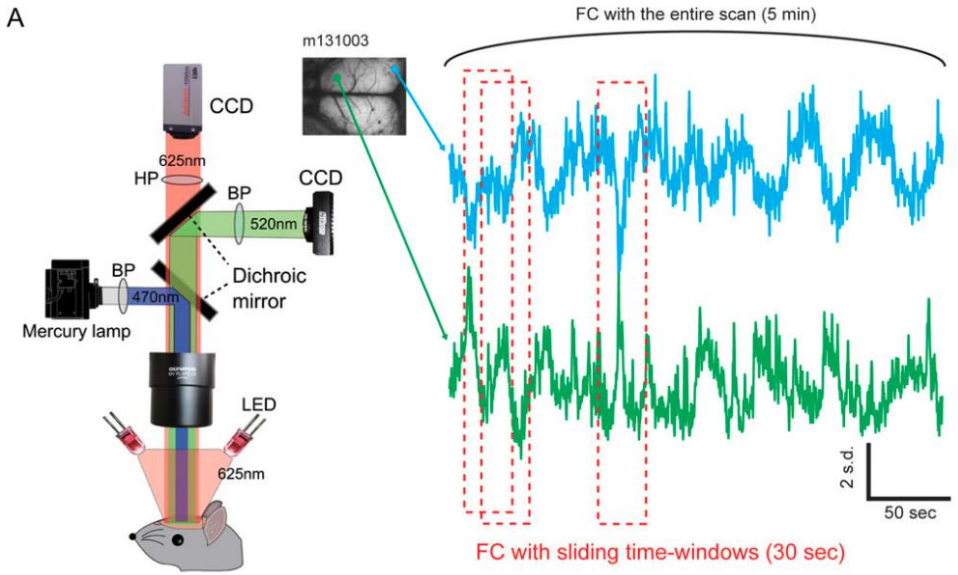


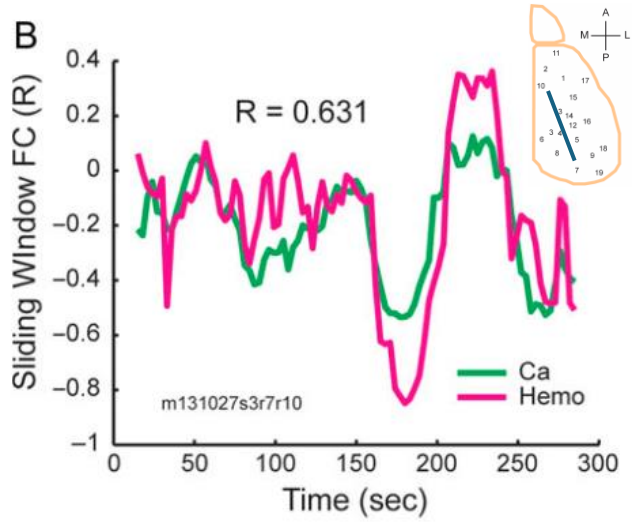
"...Beyond sampling variability, the largest part of observed "dynamics" during rest is attributable to head motion. An additional component of dynamic variability during rest is attributable to fluctuating sleep state. Thus, aside from the preceding explanatory factors, a single correlation structure—as opposed to a sequence of distinct correlation structures—may adequately describe the resting state as measured by BOLD fMRI..."

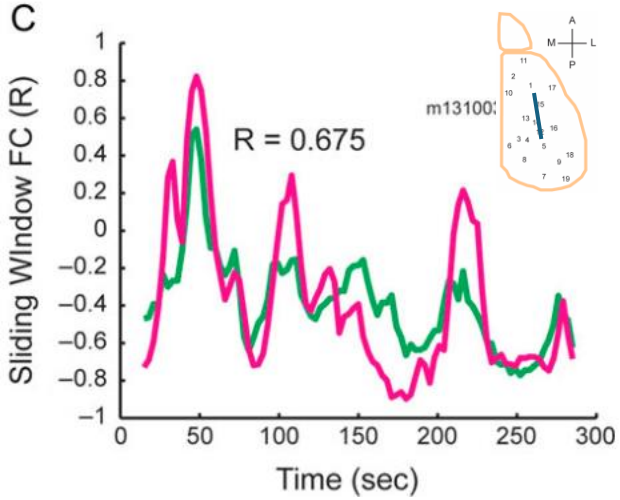
Laumann T. et al. " On the stability of BOLD fMRI Correlations" (2016) Cerebral Cortex

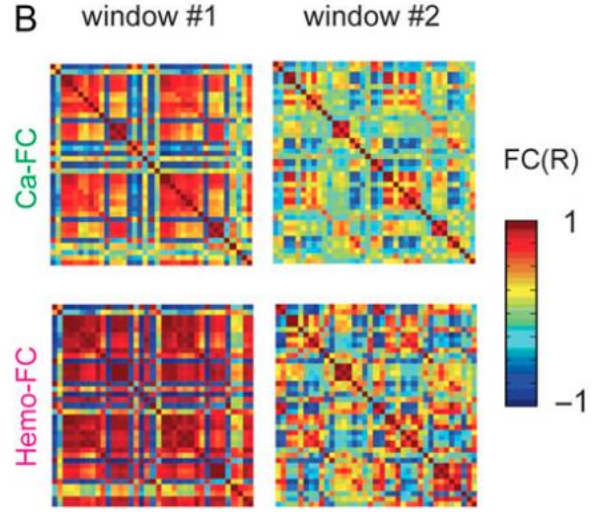
CONTROVERSY: Is it meaningful/neuronally driven?

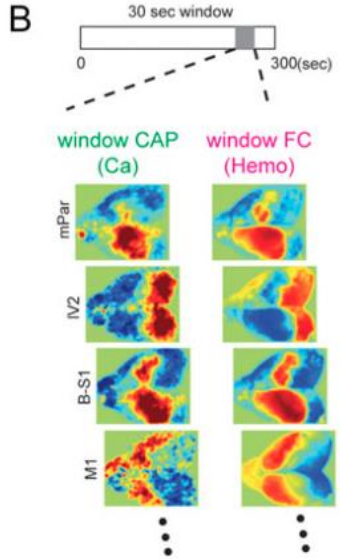
"...using simultaneous imaging of neuronal calcium and hemodynamic signals in mice and found coordinated temporal dynamics of calcium FC and hemodynamic FC measured in the same short time windows... Finally, we show that the observed dynamics of FC cannot be fully accounted for by simulated data assuming stationary FC. These results provide evidence for the neuronal origin of dynamic FC and further suggest that information relevant to FC is condensed in temporally sparse events that can be extracted using a small number of time points."











Matsui T. et al. "Neural Origin of the Temporal Dynamics of Spontaneous BOLD Activity Correlation" (2019) Cerebral Cortex

Learning Objectives

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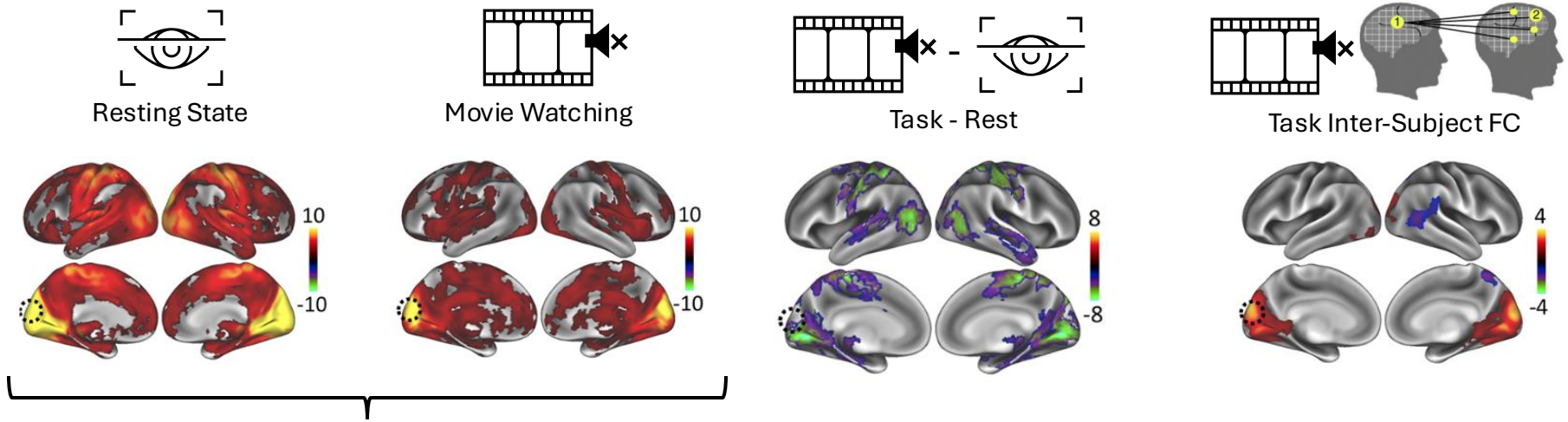
Static vs. Dynamic Functional Connectivity

How to estimate Dynamic Functional Connectivity

Special Considerations for task-based studies

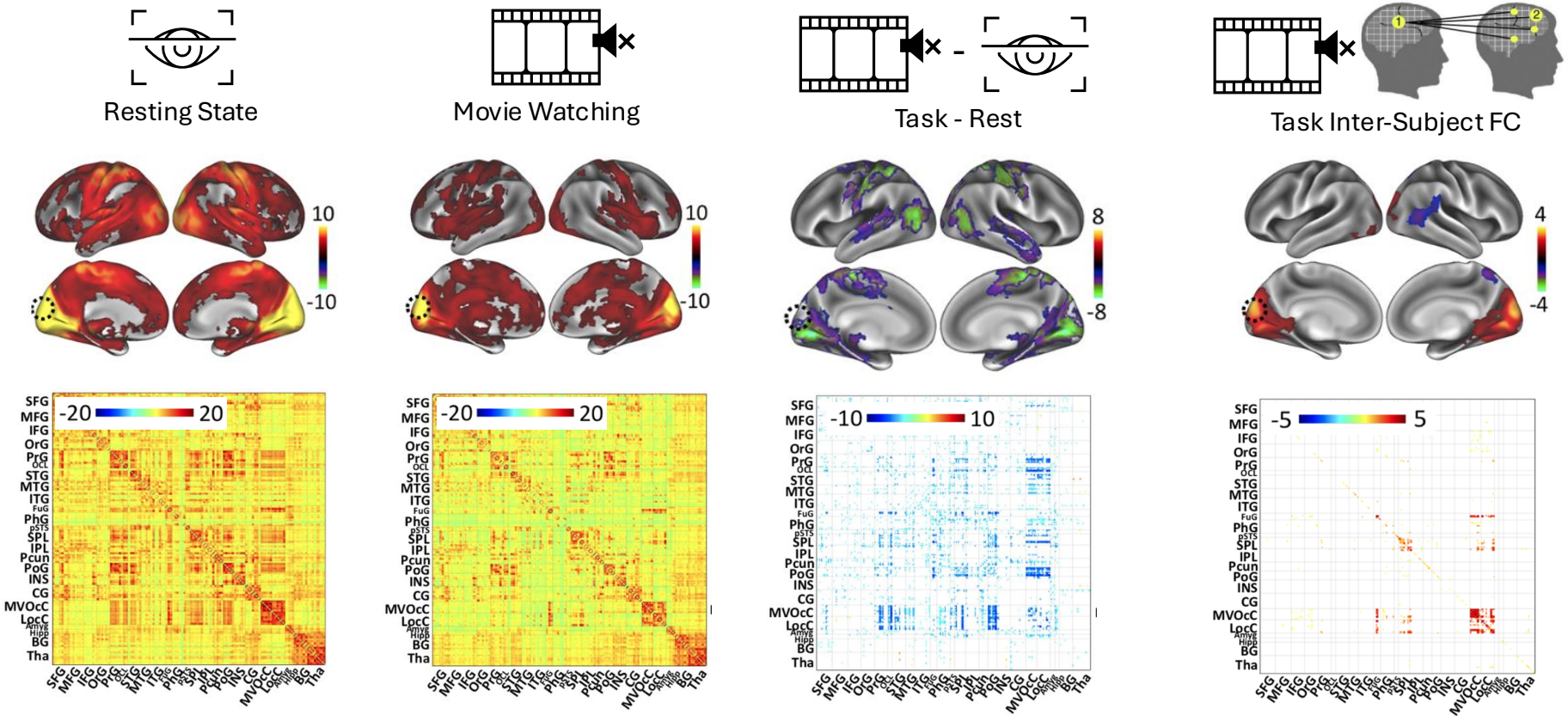
Functional Connectivity (Static & Time-varying) in Task



"…one should not at first entertain too high hopes with regard to this [being able to demonstrate the influence of intellectual work over the human encephalogram], because mental work, as I explained elsewhere, adds only a small increment to the cortical work which is going on continuously and not only in the waking state." Hans Berger (1929)

Lynch et al. "Task-evoked functional connectivity does not explain functional connectivity differences between rest and task" (2018) Human Brain Mapping

Functional Connectivity (Static & Time-varying) in Task



Spontaneous Activity

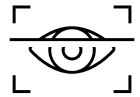
Spontaneous & Task-evoked Activity

Δ-Spontaneous & Task-evoked Activity

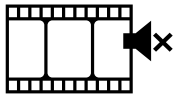
Task-evoked Activity

Lynch et al. "Task-evoked functional connectivity does not explain functional connectivity differences between rest and task" (2018) Human Brain Mapping

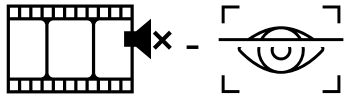
Functional Connectivity (Static & Time-varying) in Task



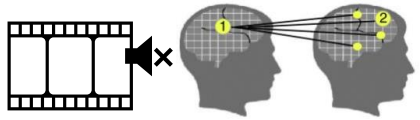
Resting State



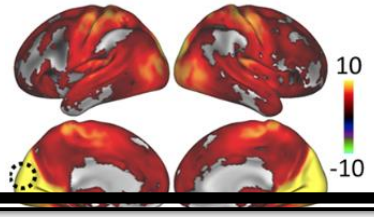
Movie Watching

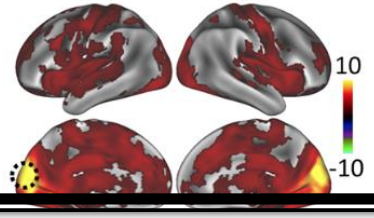


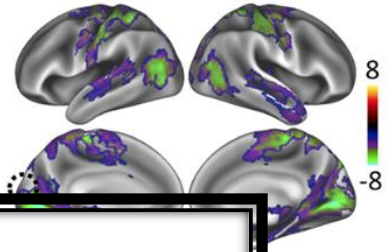
Task - Rest

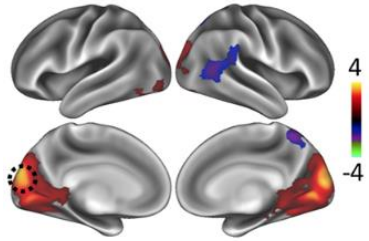


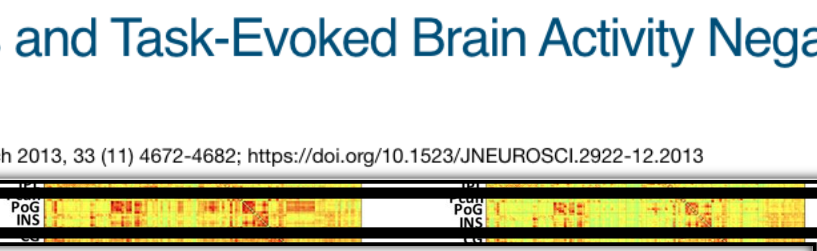
Task Inter-Subject FC

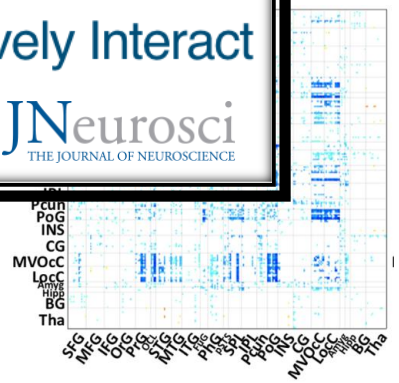


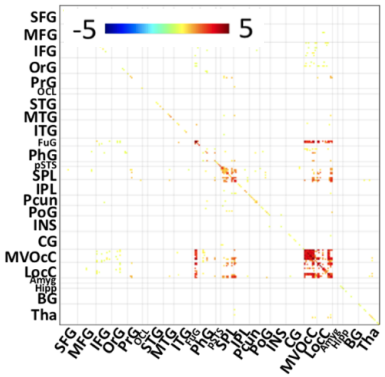












Articles, Behavioral/Cognitive

Spontaneous and Task-Evoked Brain Activity Negatively Interact

Biyu J. He

Journal of Neuroscience 13 March 2013, 33 (11) 4672-4682; https://doi.org/10.1523/JNEUROSCI.2922-12.2013

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RESEARCH ARTICLE

Task-evoked activity quenches neural correlations and variability across cortical areas

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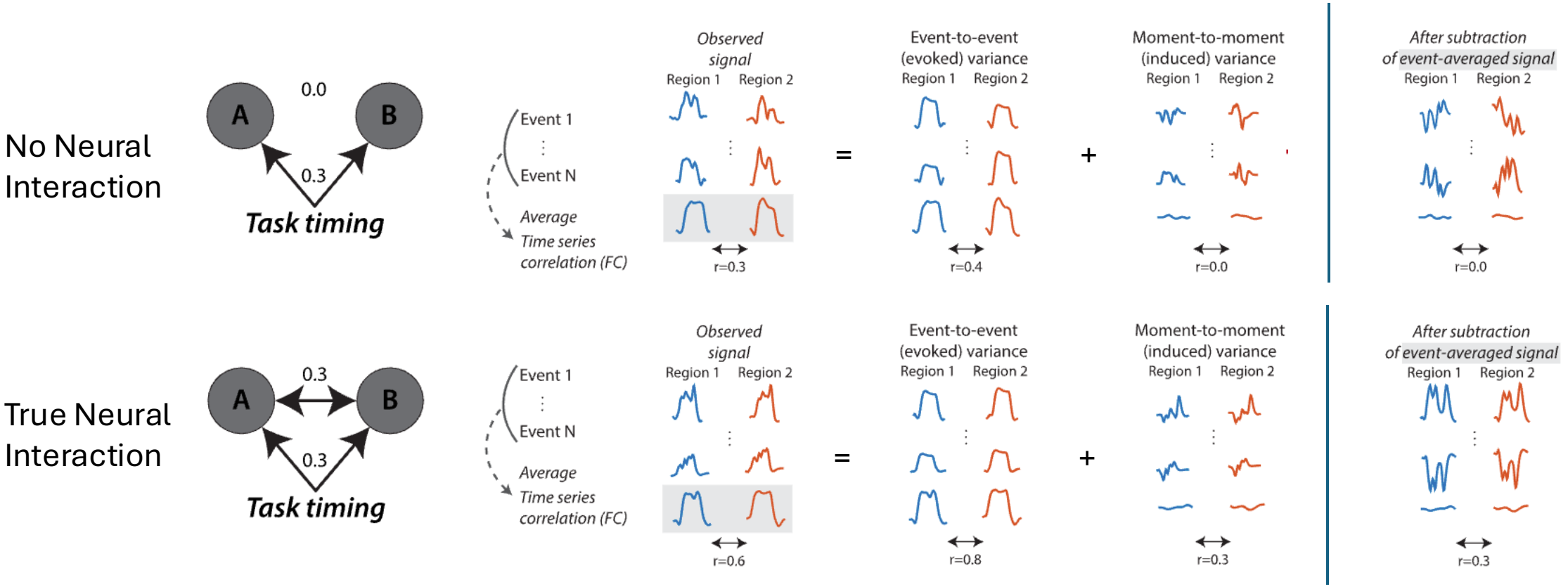
Δ-Spontaneous & Task-evoked Activity

Task-evoked Activity

Lynch et al. "Task-evoked functional connectivity does not explain functional connectivity differences between rest and task" (2018) Human Brain Mapping

Functional Connectivity (Static & Time-varying) in Task

Two regions exhibiting elevated signal magnitudes during a task, relative to a baseline, does not necessarily denote communication and exchange of task-relevant information among them.

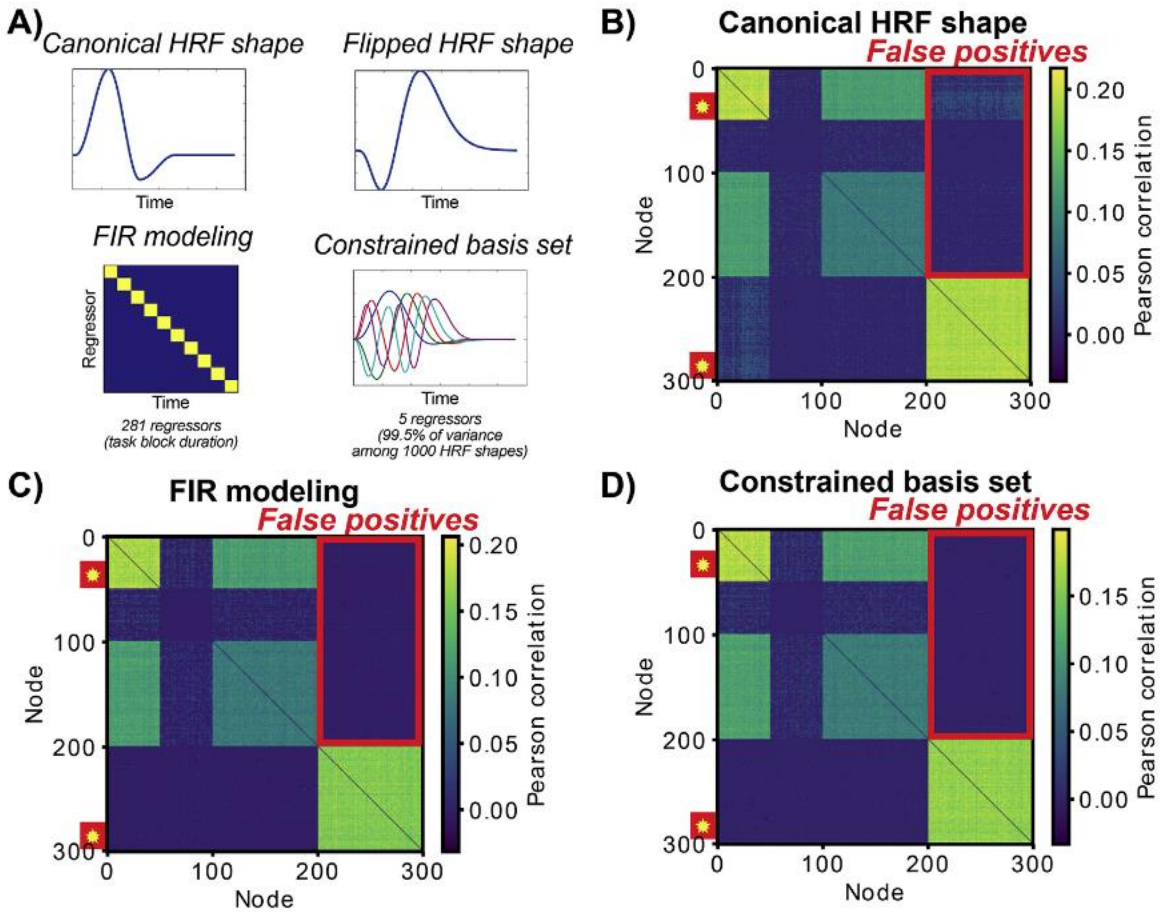


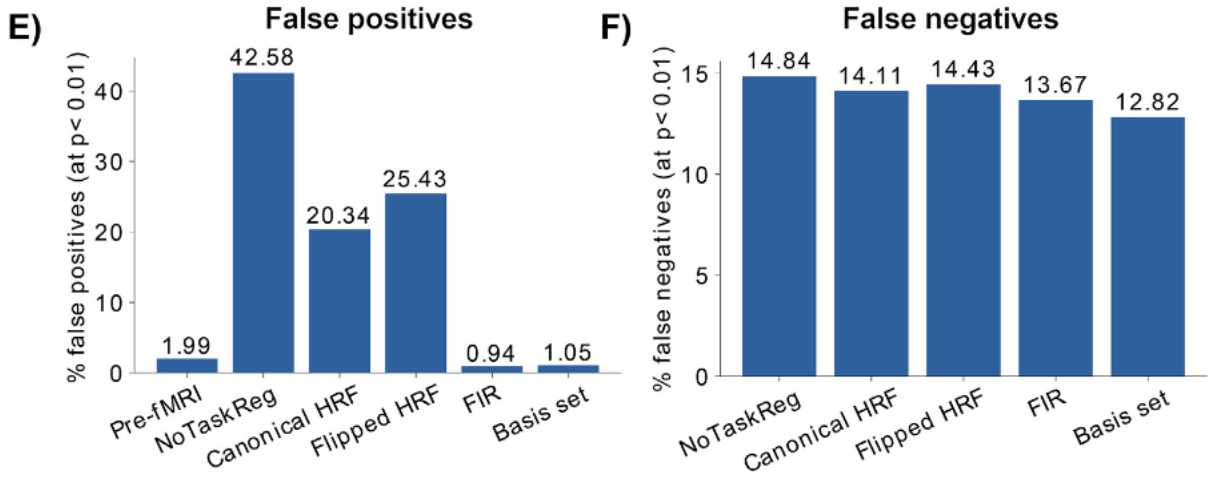
These "*first level*" effects can act as confounds for task-based dynamics by artificially inflating FC estimates during task states

Cole et al. "Task activations produce spurious but systematic inflation of task functional connectivity estimates" (2019) NeuroImage

Functional Connectivity (Static & Time-varying) in Task

"…that most standard approaches for fitting and removing mean task-evoked activations were unable to correct these inflated correlations. In contrast, methods that flexibly fit mean task-evoked response shapes effectively corrected the inflated correlations without reducing effects of interest…"



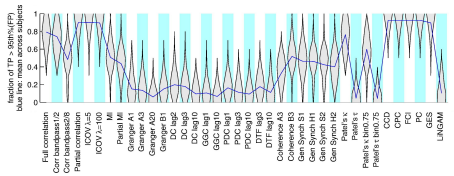


Cole et al. "Task activations produce spurious but systematic inflation of task functional connectivity estimates" (2019) NeuroImage

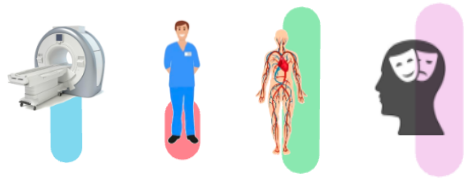
Conclusions / Summary

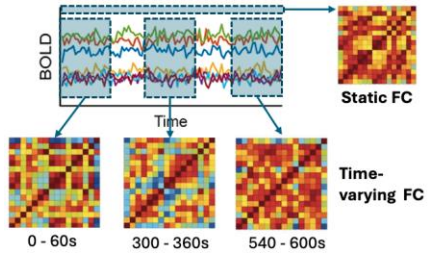
"Functional connectivity is simply a statement about the observed correlations; it does not provide any direct insight into how these correlations are mediated." Friston (1994)

ICA

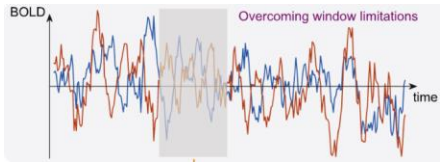


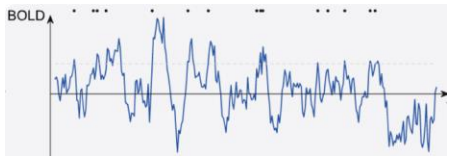
> 10 mins

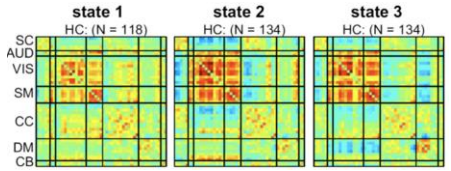




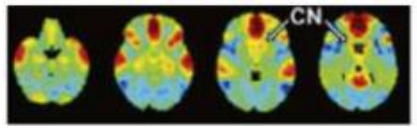
CONTROVERSY: Is it meaningful/neuronally driven?

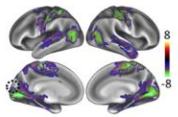


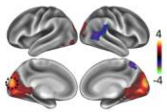




CAPs

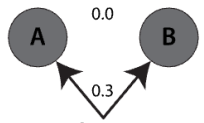




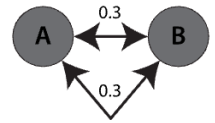


$$REST: y_i(t) = s_i(t) + n_i(t)$$

$$TASK: y_i(t) = s_i(t) + t_i(t) + F(s_i(t), t_i(t)) + n_i(t)$$



VS



Thank you / Questions