Dynamic Connectivity: Is it real? Is it useful? How do we extract information?

Javier Gonzalez-Castillo, SFIM, NIMH, NIH, Bethesda, MD

August 29^{th} , NIMH Summer fMRI Course

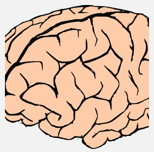
Main Questions we will *<u>try</u>* to address

?

What is dynamic FC?

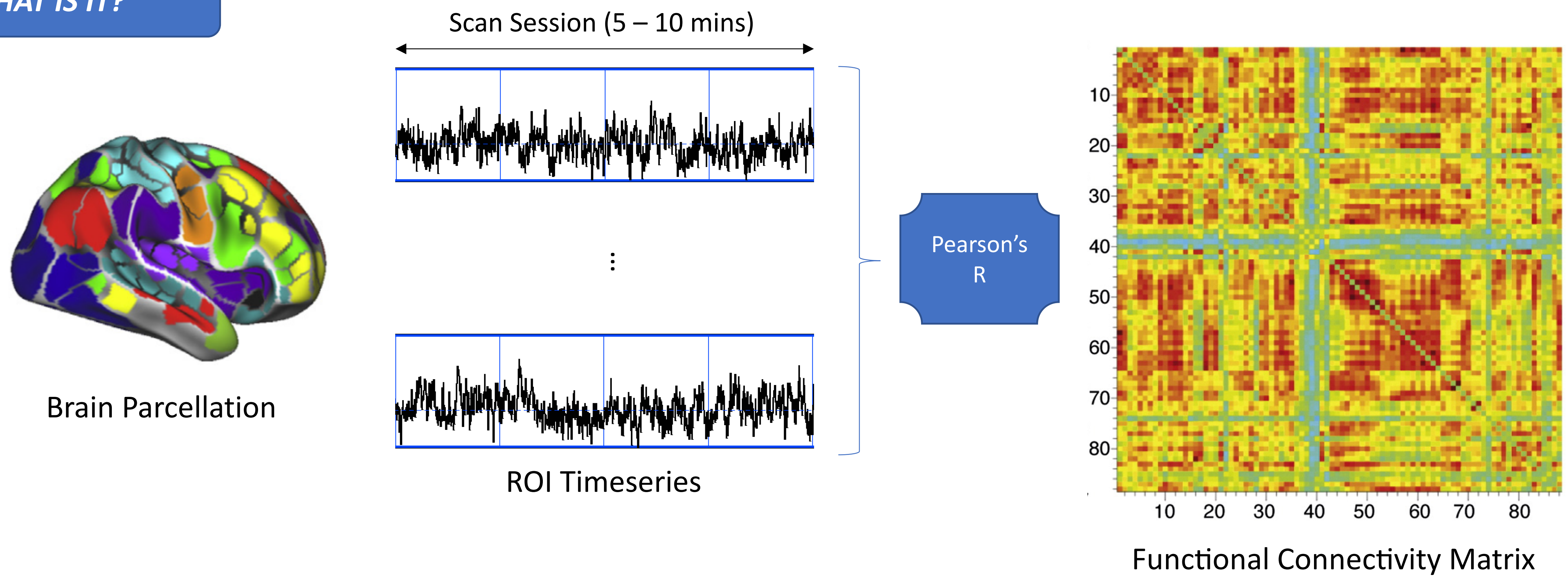
How do we measure dynamic FC?

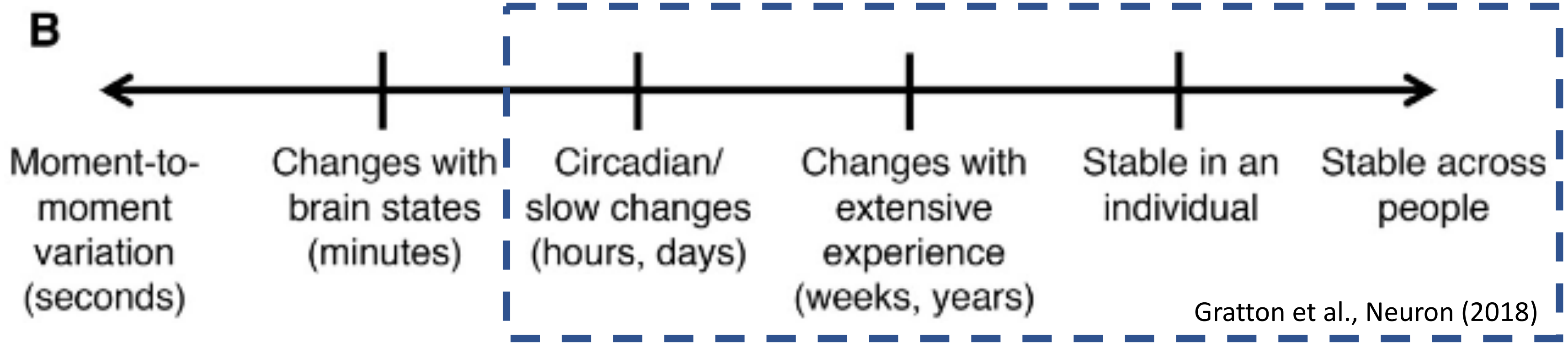
Is dynamic FC neuronally and behaviorally meaningful?



What have we learned? Key Observations / Conclusions

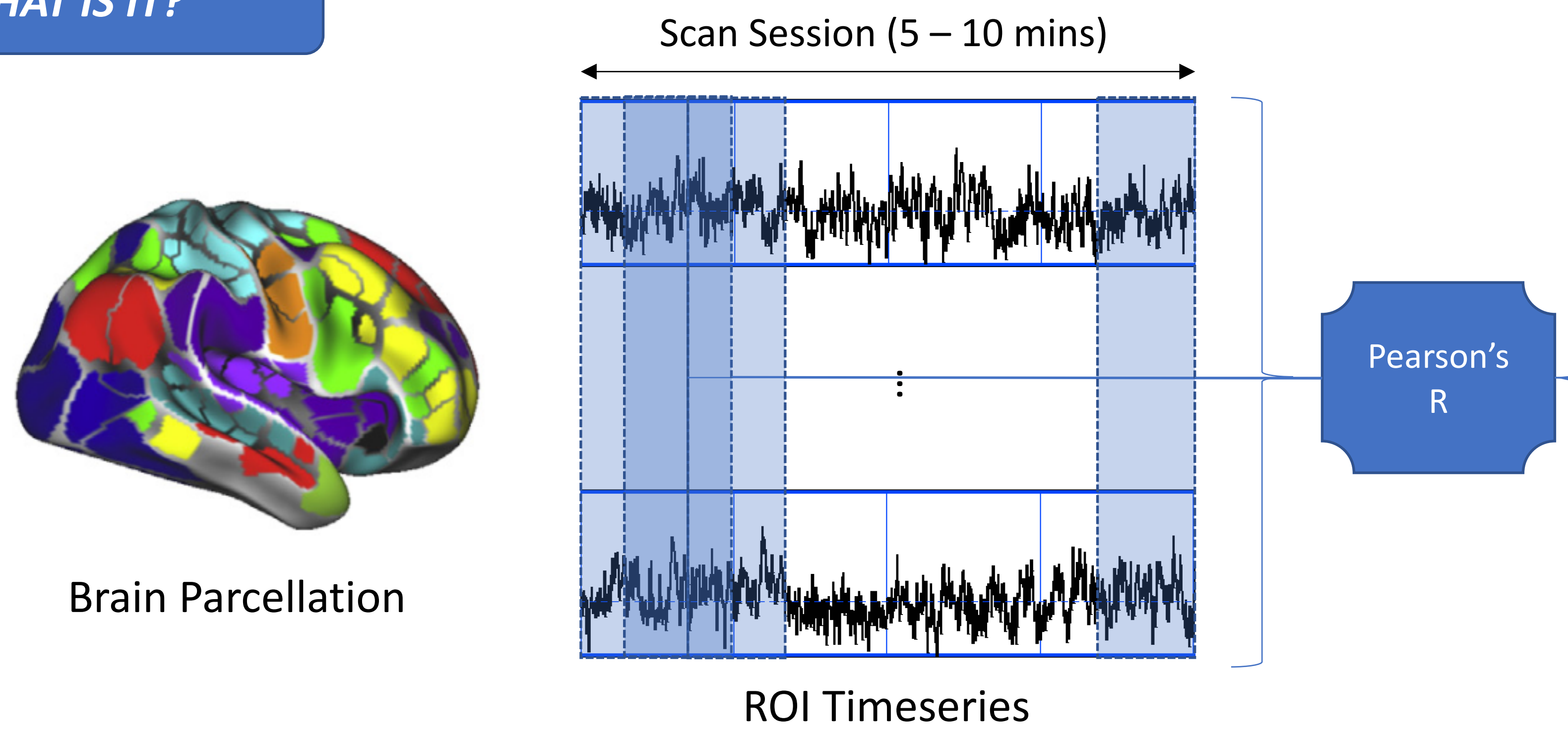
WHAT IS IT?

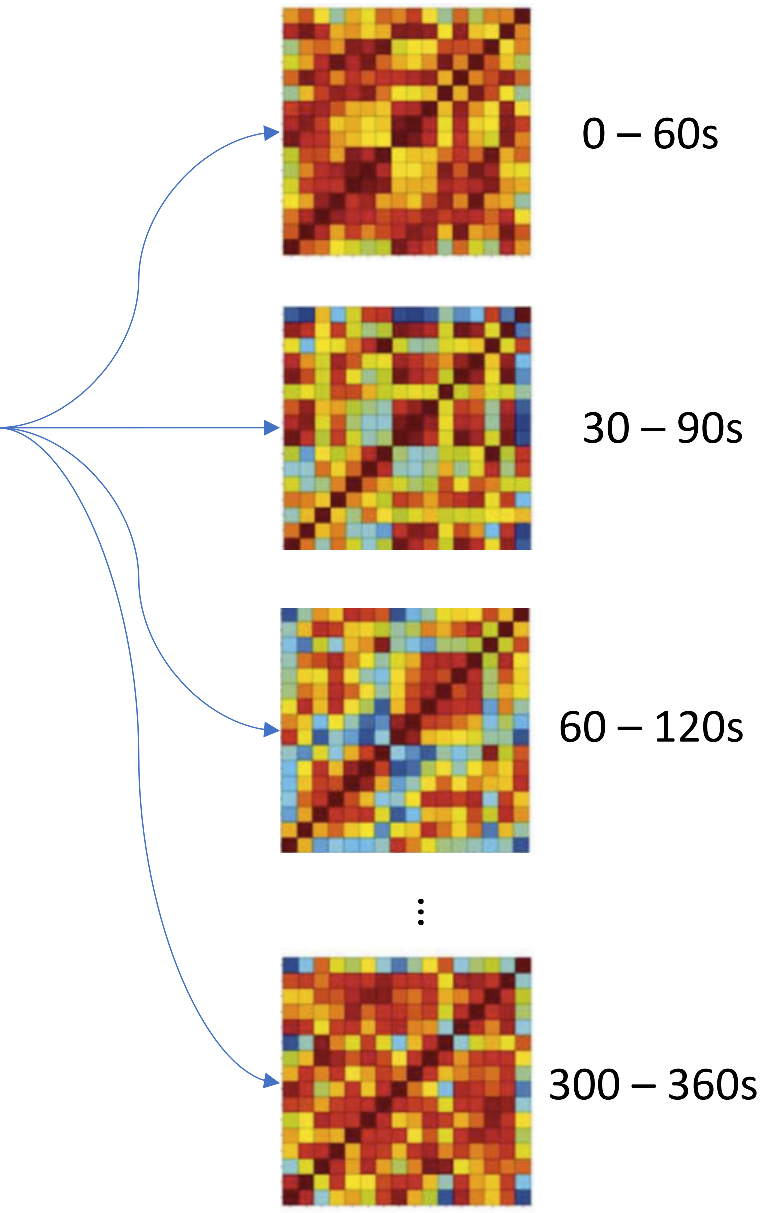


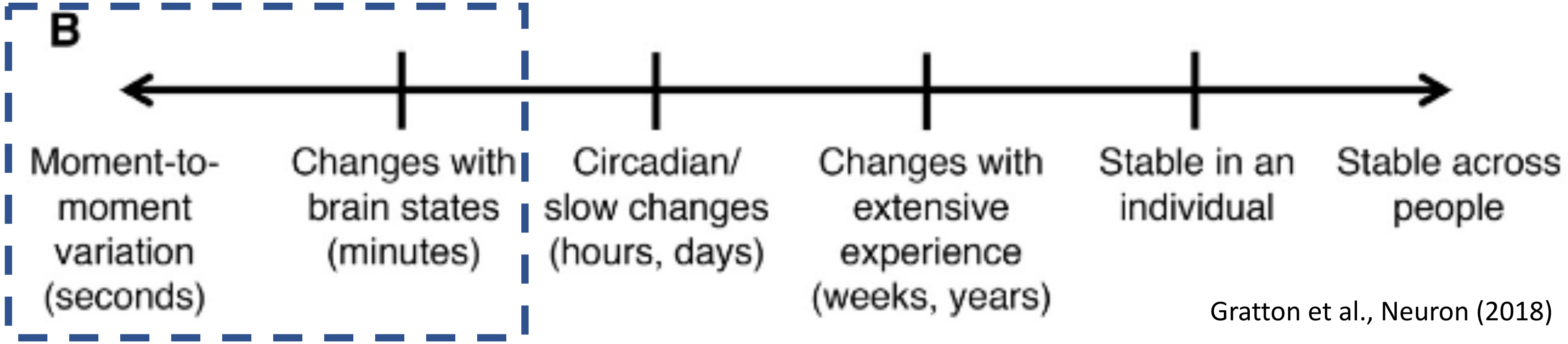


Gratton et al., Neuron (2018)

WHAT IS IT?

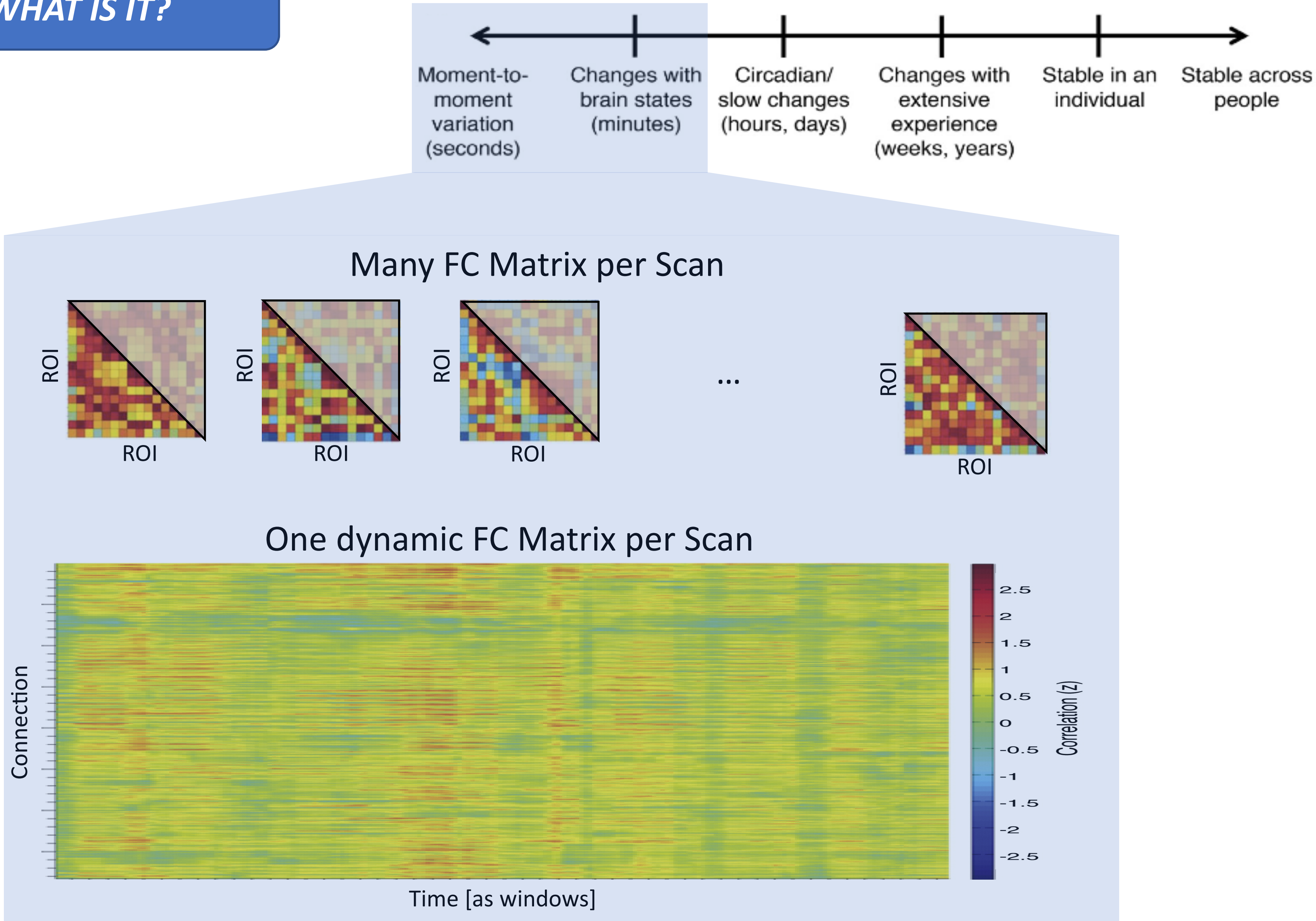






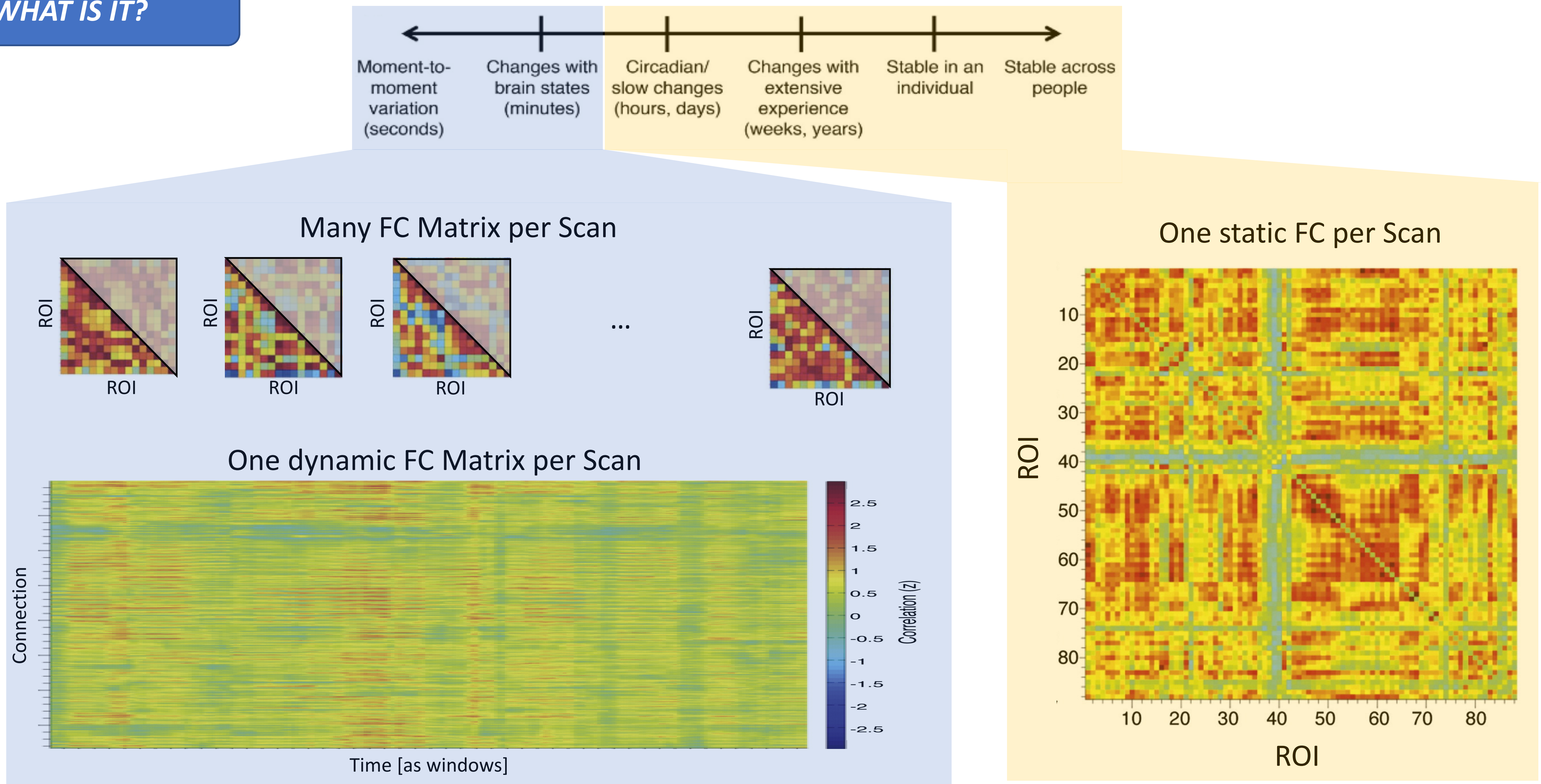
Gratton et al., Neuron (2018)

WHAT IS IT?



Moment-to-moment variation (seconds)
Changes with brain states (minutes)
Circadian/ slow changes (hours, days)
Changes with extensive experience (weeks, years)
Stable in an individual
Stable across people
Many FC Matrix per Scan
ROI
ROI
ROI
ROI
ROI
ROI
...
ROI
ROI
One dynamic FC Matrix per Scan
Connection
Time [as windows]
2.5
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
Correlation (z)

WHAT IS IT?



DYNAMIC FUNCTIONAL CONNECTIVITY

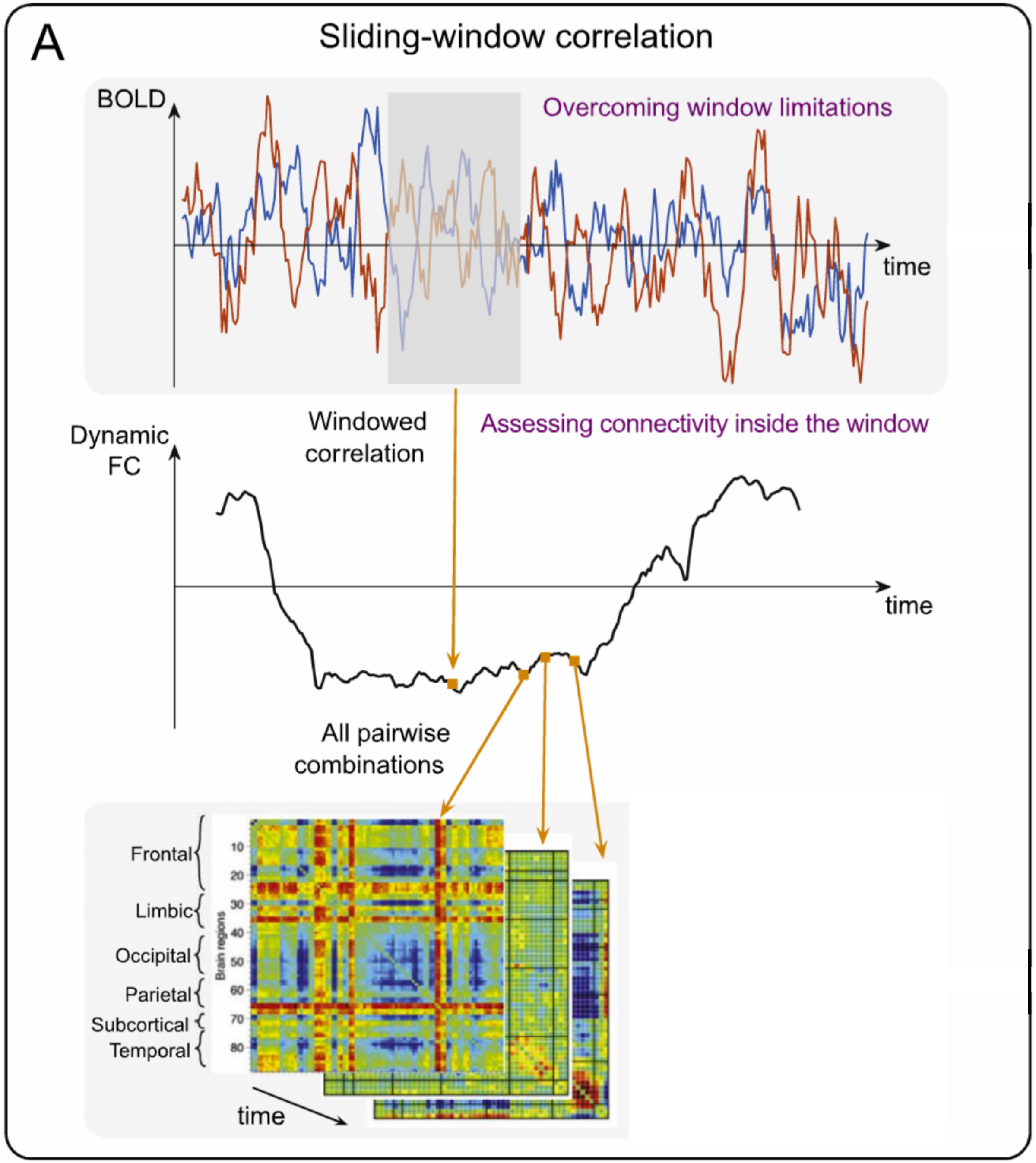
STATIC FUNCTIONAL CONNECTIVITY

WHAT IS IT?

	STATIC FUNCTIONAL CONNECTIVITY	**DYNAMIC FUNCTIONAL CONNECTIVITY**	
TIME-VARYING AT SHORT TEMPORAL SCALE	One FC configuration per scan	Several FC configurations per scan	Sliding Windows Brain States CAPs QPPs
SYSTEMS THEORY	Invariant to temporal re-ordering of time points (memoryless)	Non-Invariant to temporal re-ordering of time points (memory)	Autocorrelation Models
STATISTICS	Summary statistics are not time dependent	Summary statistics are time dependent	Kurtosis

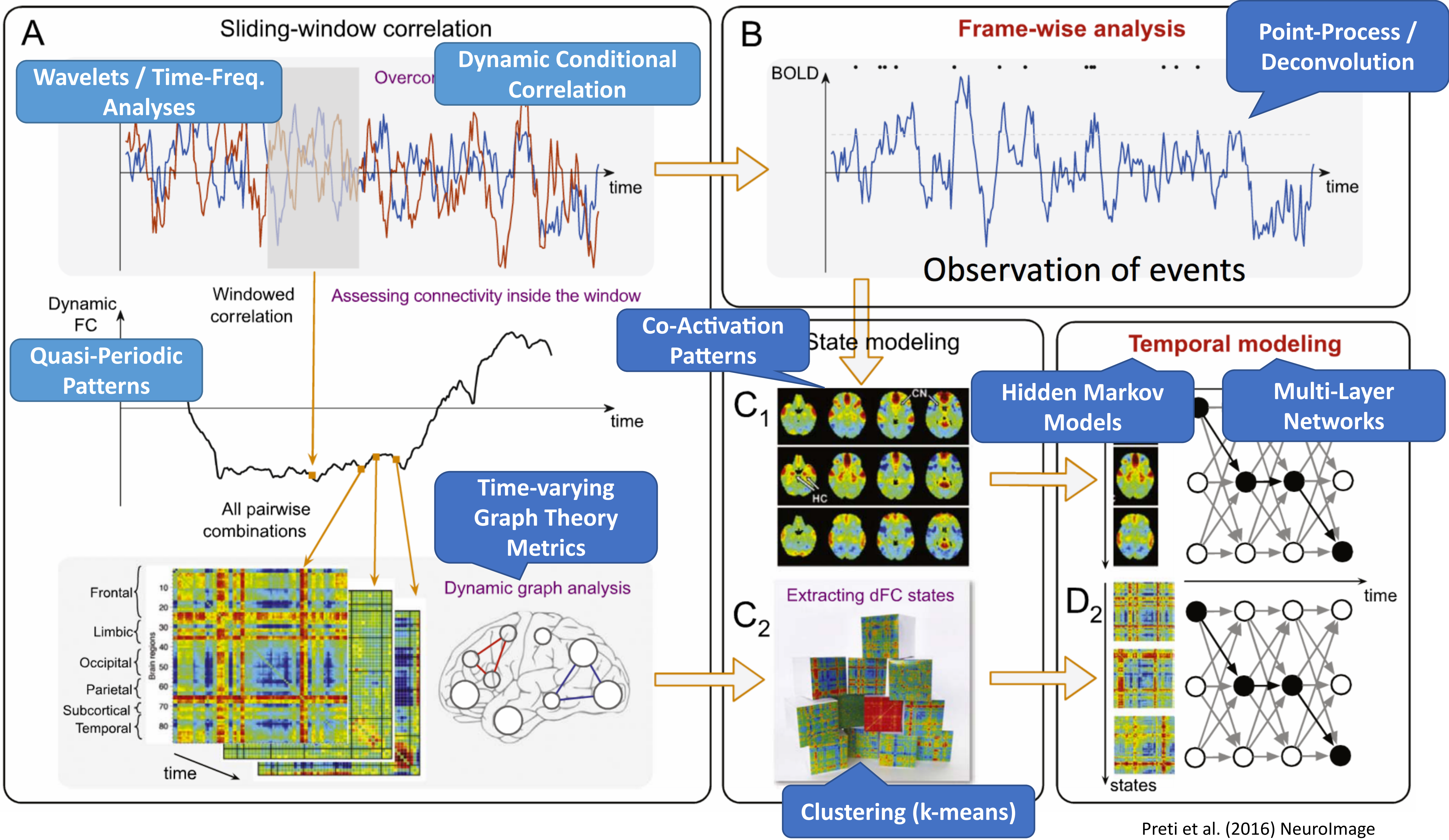
Liegeois R. et al. (2017) NeuroImage

HOW TO MEASURE IT?



Preti et al. (2016) NeuroImage

HOW TO MEASURE IT?

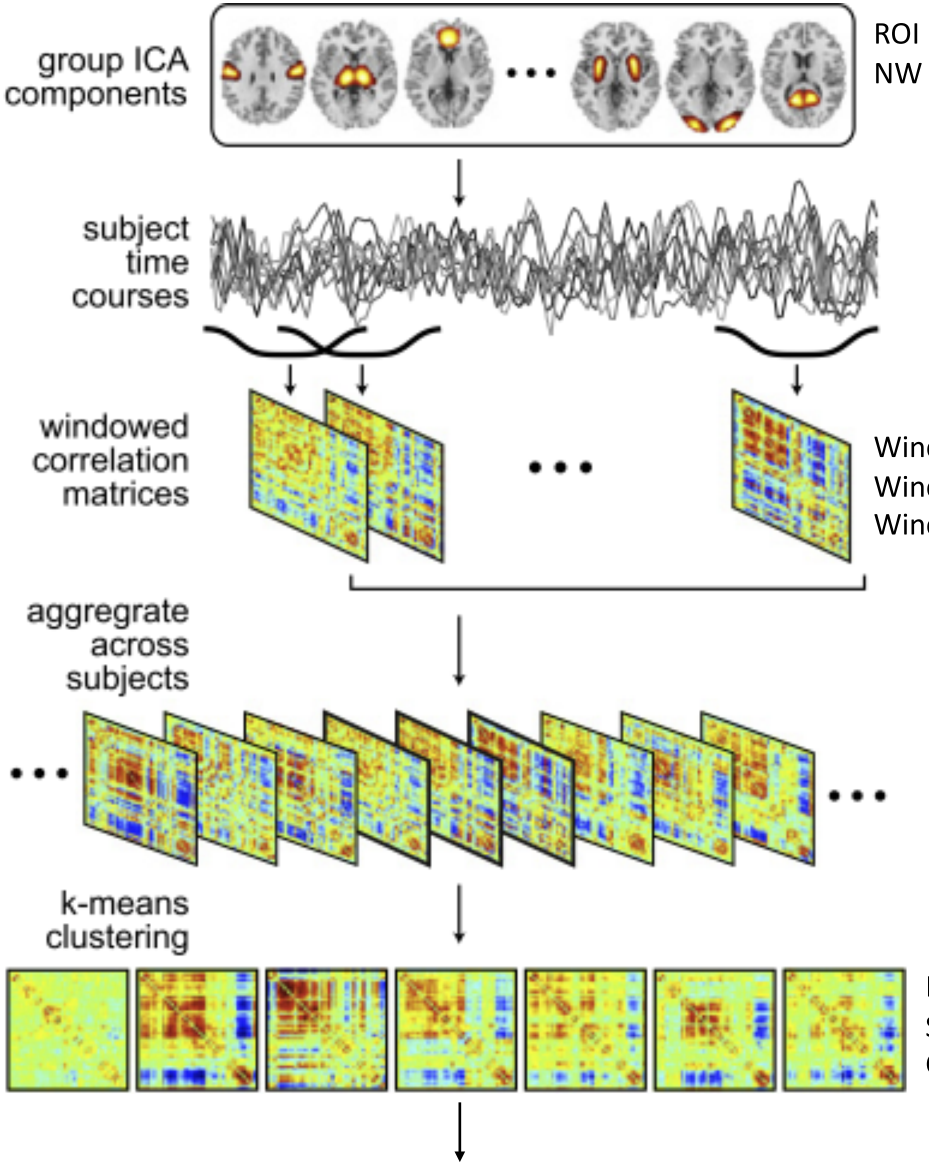


Preti et al. (2016) NeuroImage

HOW TO MEASURE IT?

FC State Models

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



ROI Level,
NW Level

Window Length,
Window Step,
Window Size

How to choose k?
Similarity Metric?
Clustering Algorithm?

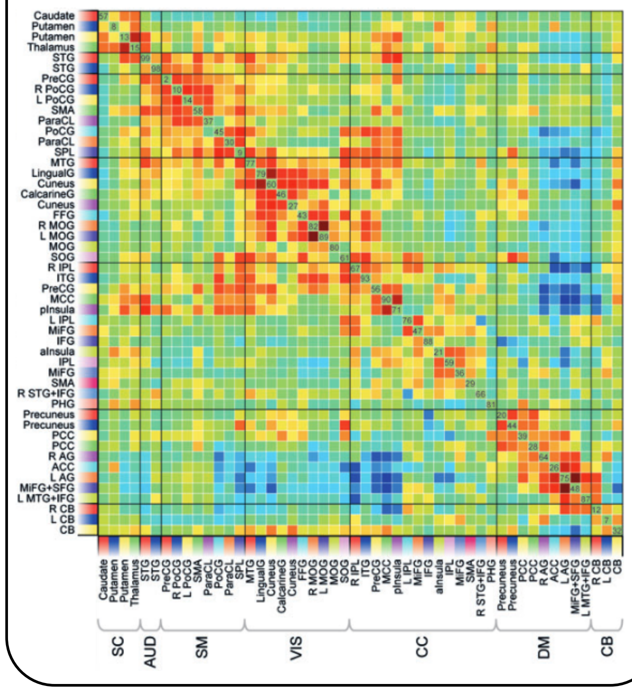
Summary Statistics (e.g., dwell times, number of transitions, trajectories)

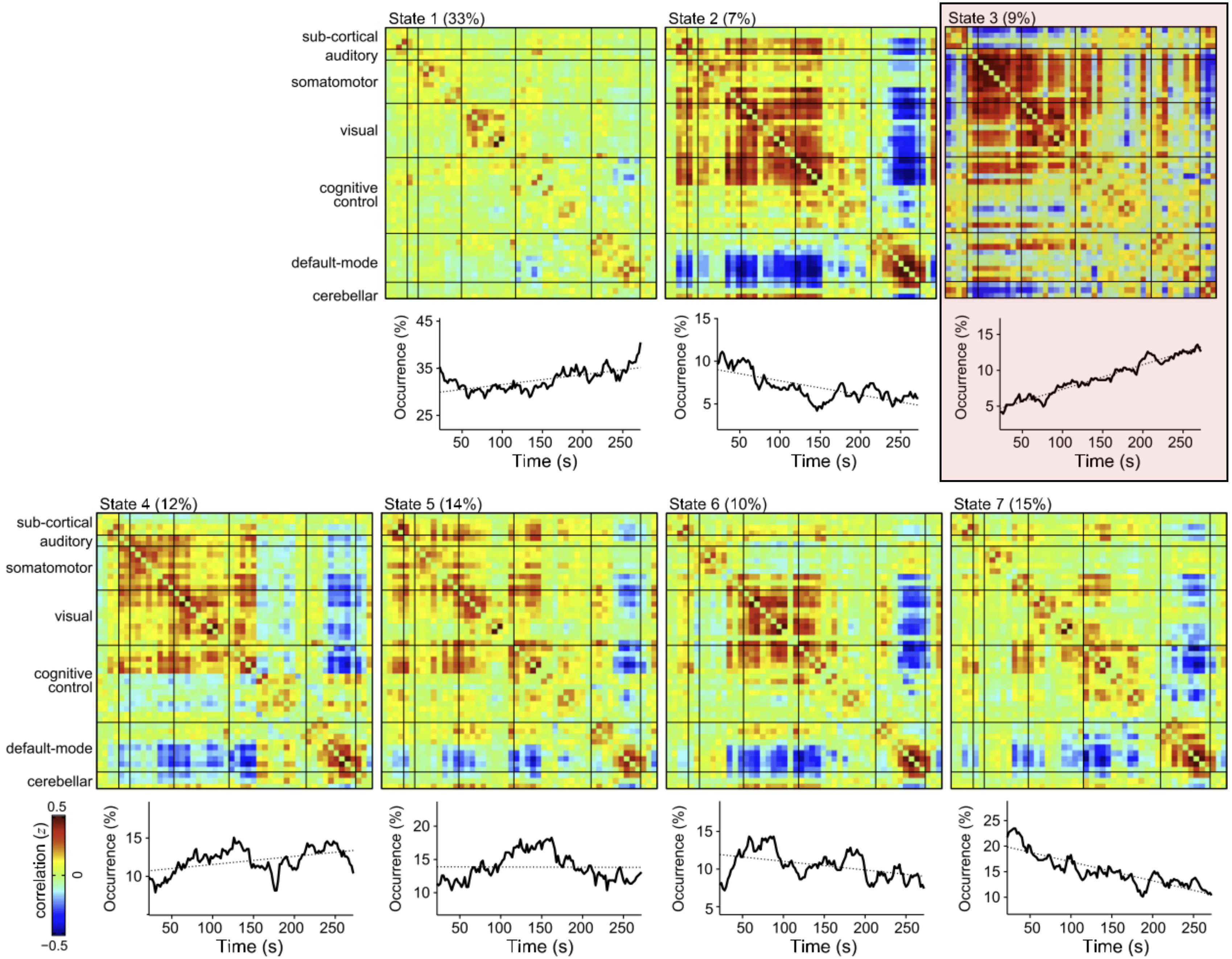
Allen et al. Cer. Cortex, 2014

HOW TO MEASURE IT?

FC State Models

STATIC FC MATRIX

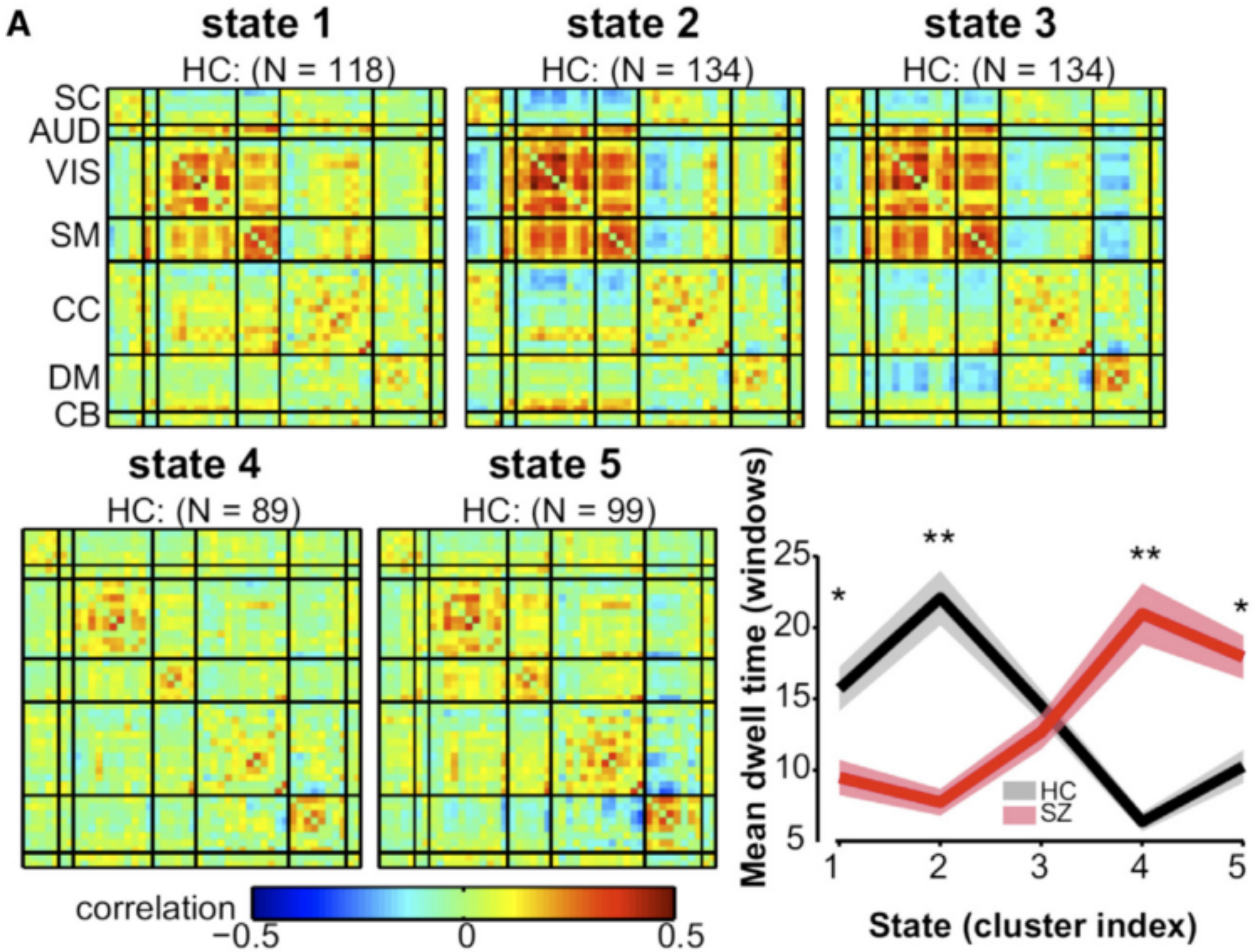




Allen et al. Cer. Cortex, 2014

HOW TO MEASURE IT?

FC State Models



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.

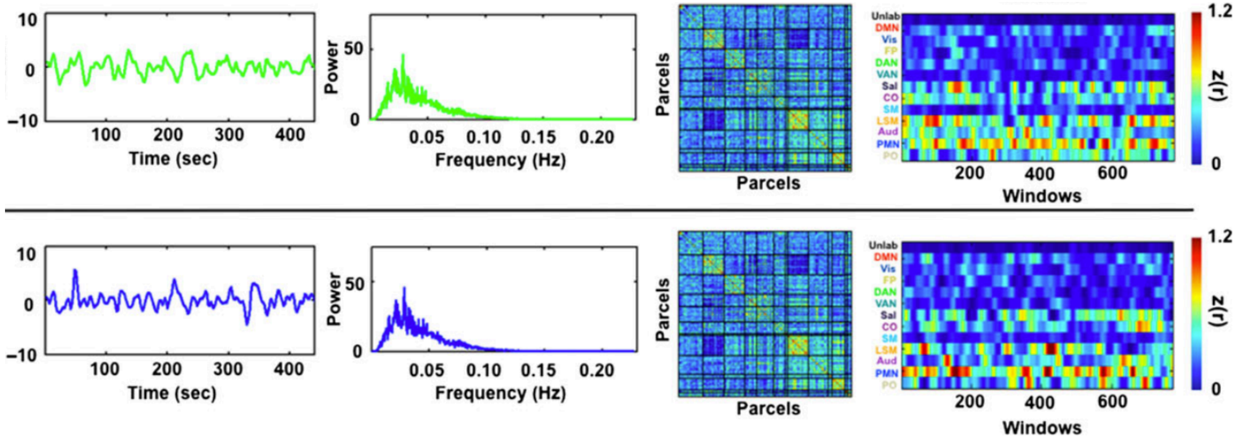
Damaraju et al. NeuroImage Clinical, 2014

HOW TO MEASURE IT?

FC State Models

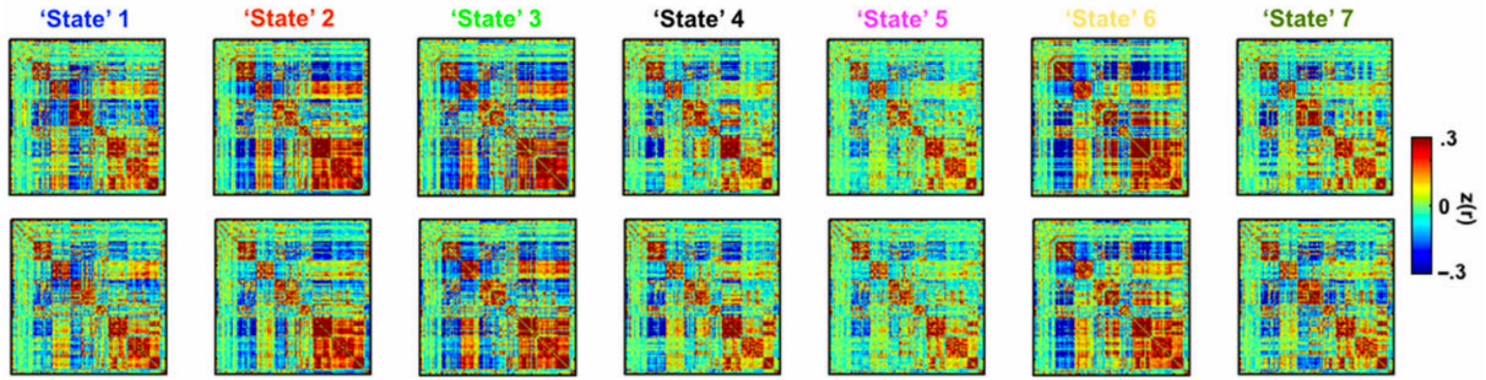
Null Data (Stationary)

Real fMRI Data



Real Resting State fMRI Data

Null Data (Stationary)



"The appearance of discrete states can be generated simply by sampling variability"

Laumann T. et al. (2016) Cerebral Cortex

"Statistical stationarity does not imply the absence of evident temporal epochs [functionally relevant dynamics]"

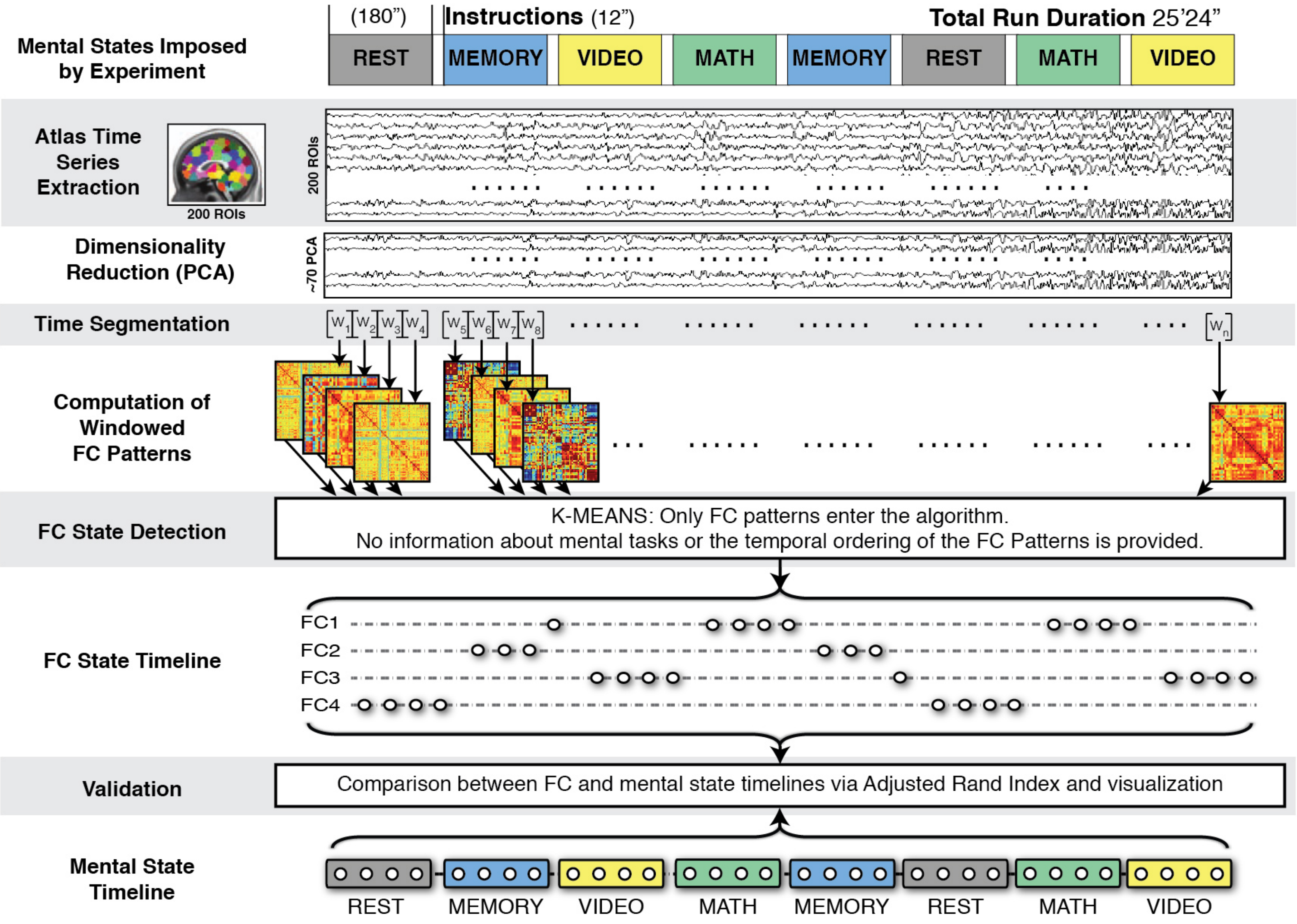
Miller R. et al. (2018) Frontiers in Neuroscience

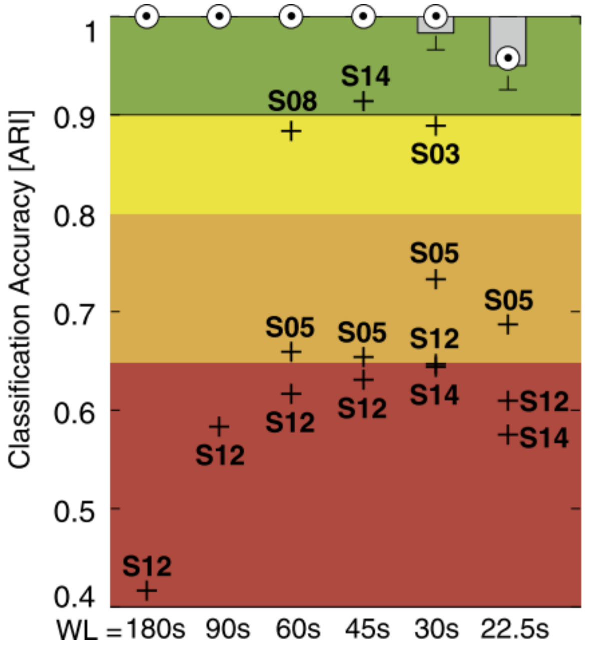
Additional References on Null Models Discussion

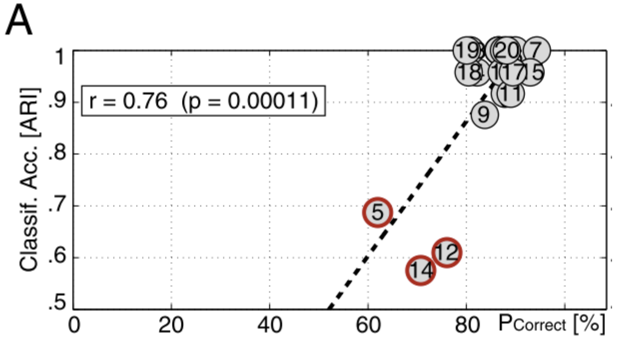
- Handwerker et al. "Periodic Changes in fMRI connectivity" (2012) NeuroImage
- Hindriks et al. "Can sliding-window correlations reveal dynamic FC in resting fMRI?" (2016) NeuroImage
- Liegeois et al. "Interpreting temporal fluctuations in resting-state FC MRI" (2017) NeuroImage

HOW TO MEASURE IT?

FC State Models



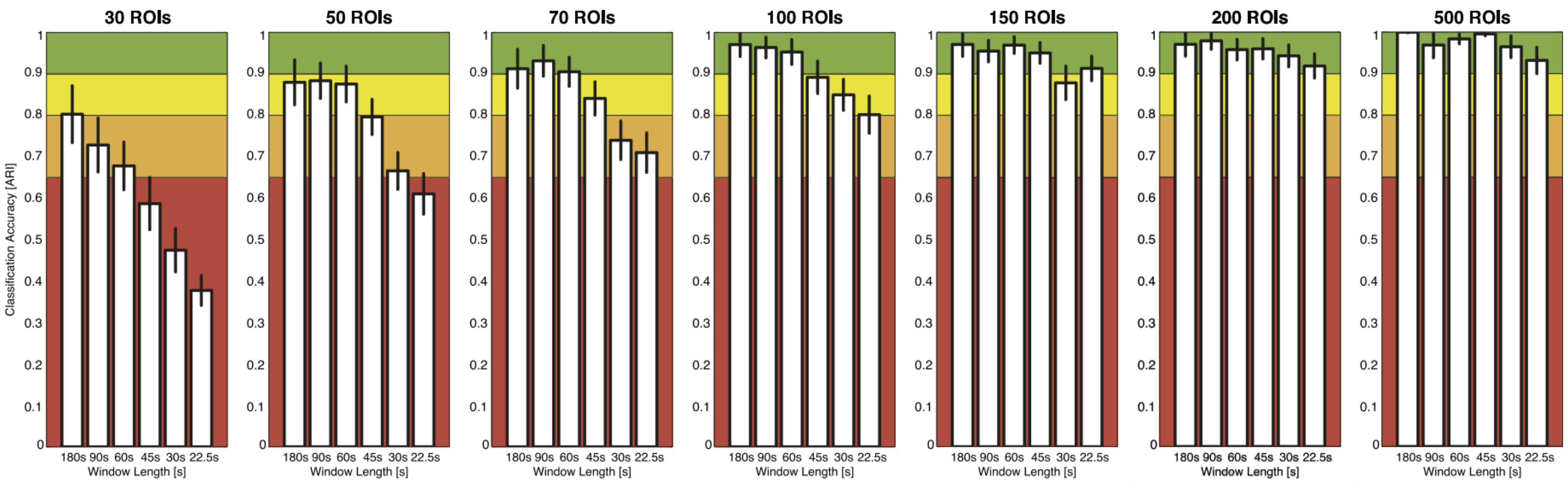




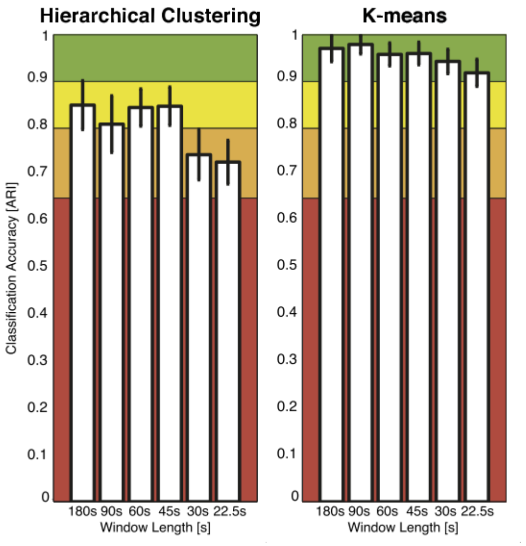
Gonzalez-Castillo J. et al. (2015) PNAS

HOW TO MEASURE IT?

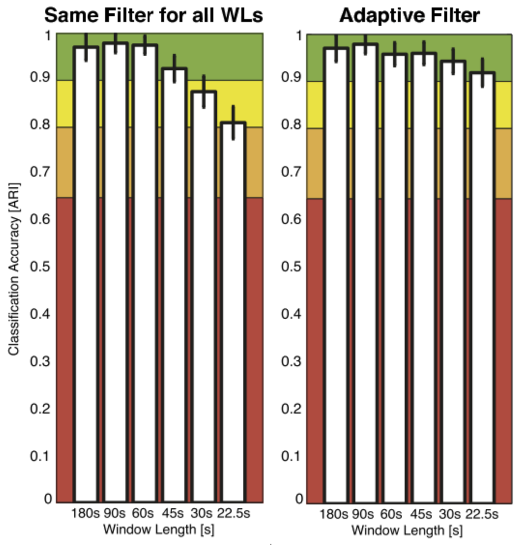
FC State Models



Parcellation



Clustering Method

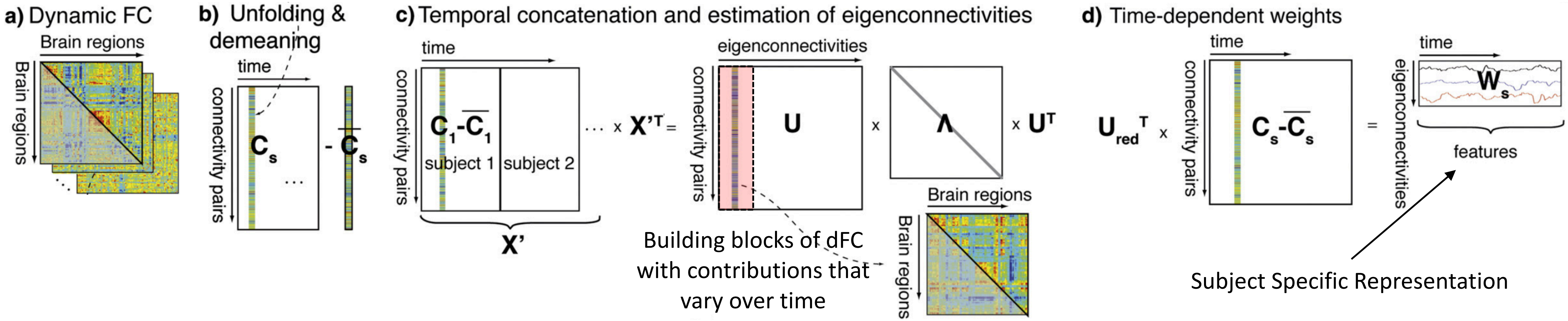


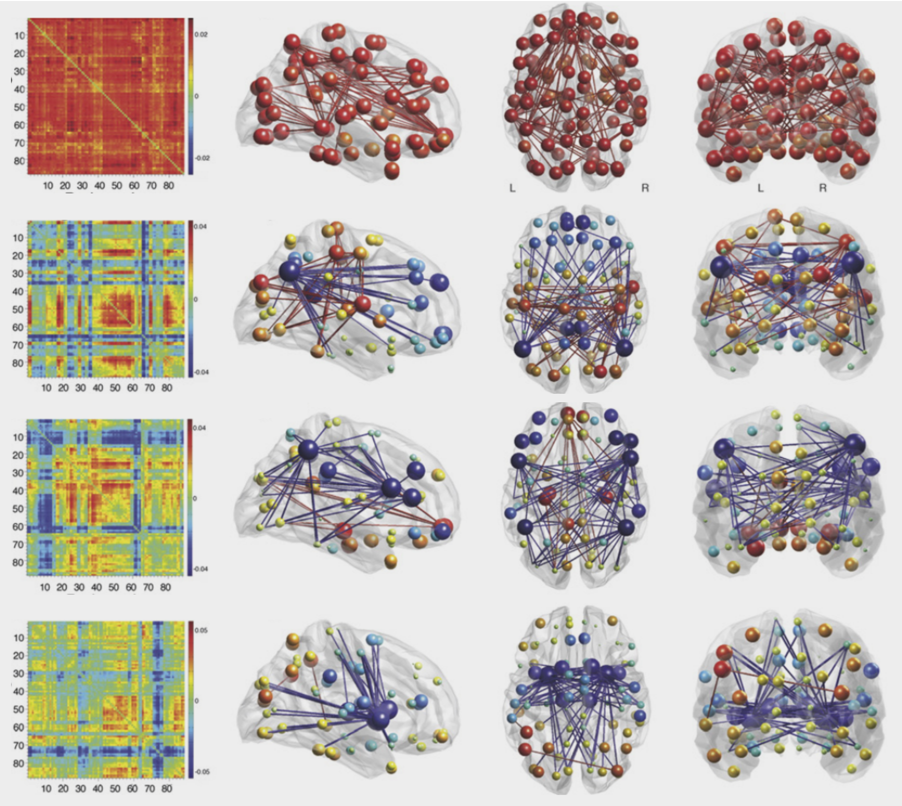
Pre-processing

Gonzalez-Castillo J. et al. (2015) PNAS

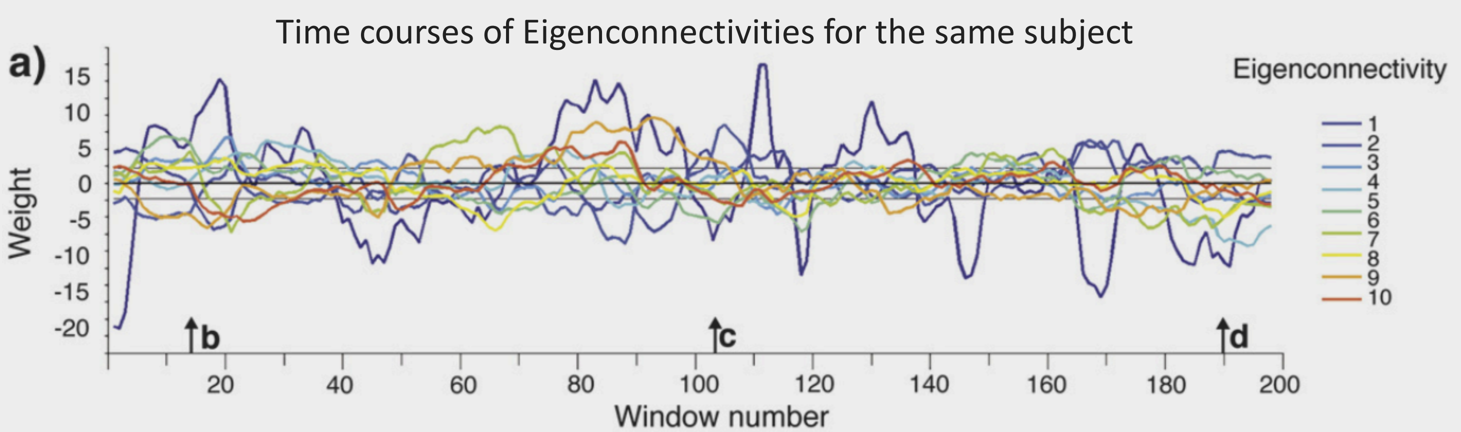
HOW TO MEASURE IT?

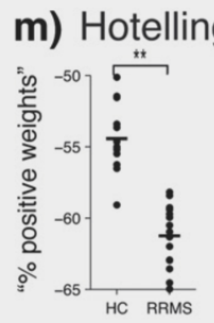
Eigenconnectivities





Exemplar Top Eigenconnectivities for 1 subject





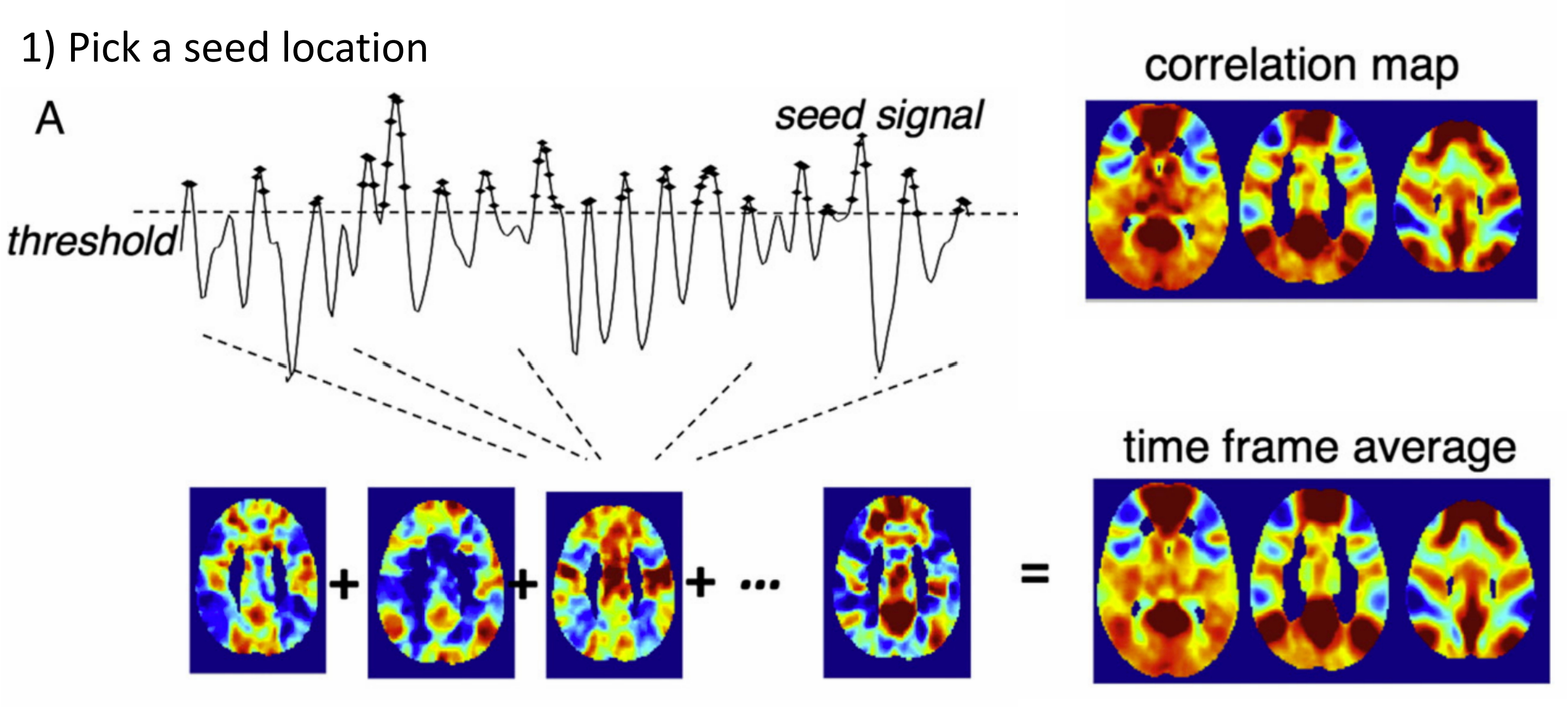
Significant differences in occupancy of eigenconnectivities between HC and Relapse-Remitting Multiple Sclerosis Patients

Leonardi N. et al. (2013) NeuroImage

ASSUMPTION: All dynamics of interest are captured by a limited number of sparse, strong and short (1TR) events

POINT-PROCESS ANALYSIS

1) Pick a seed location



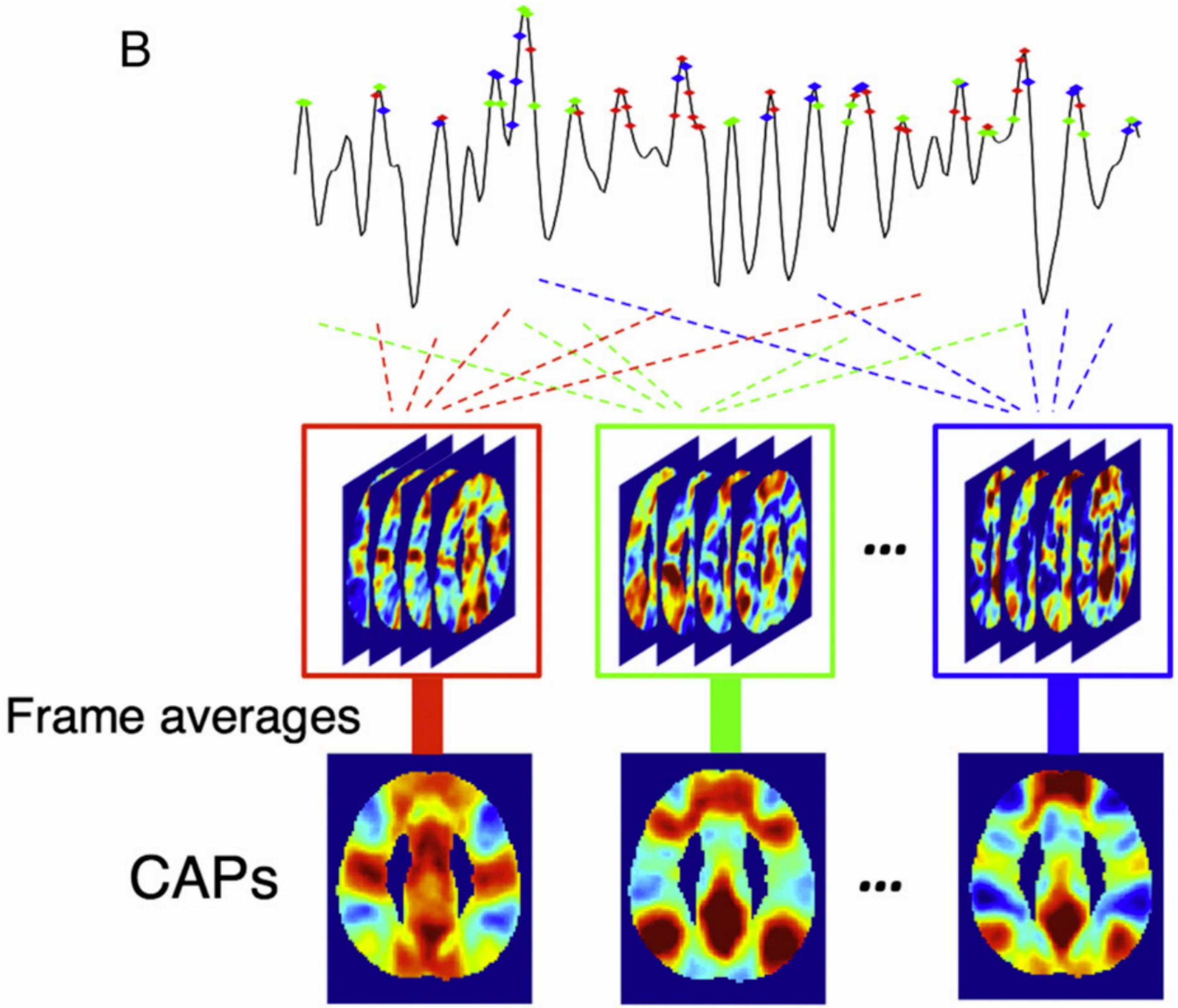
2) Extract Maps for above-threshold time points

3) Average All Maps

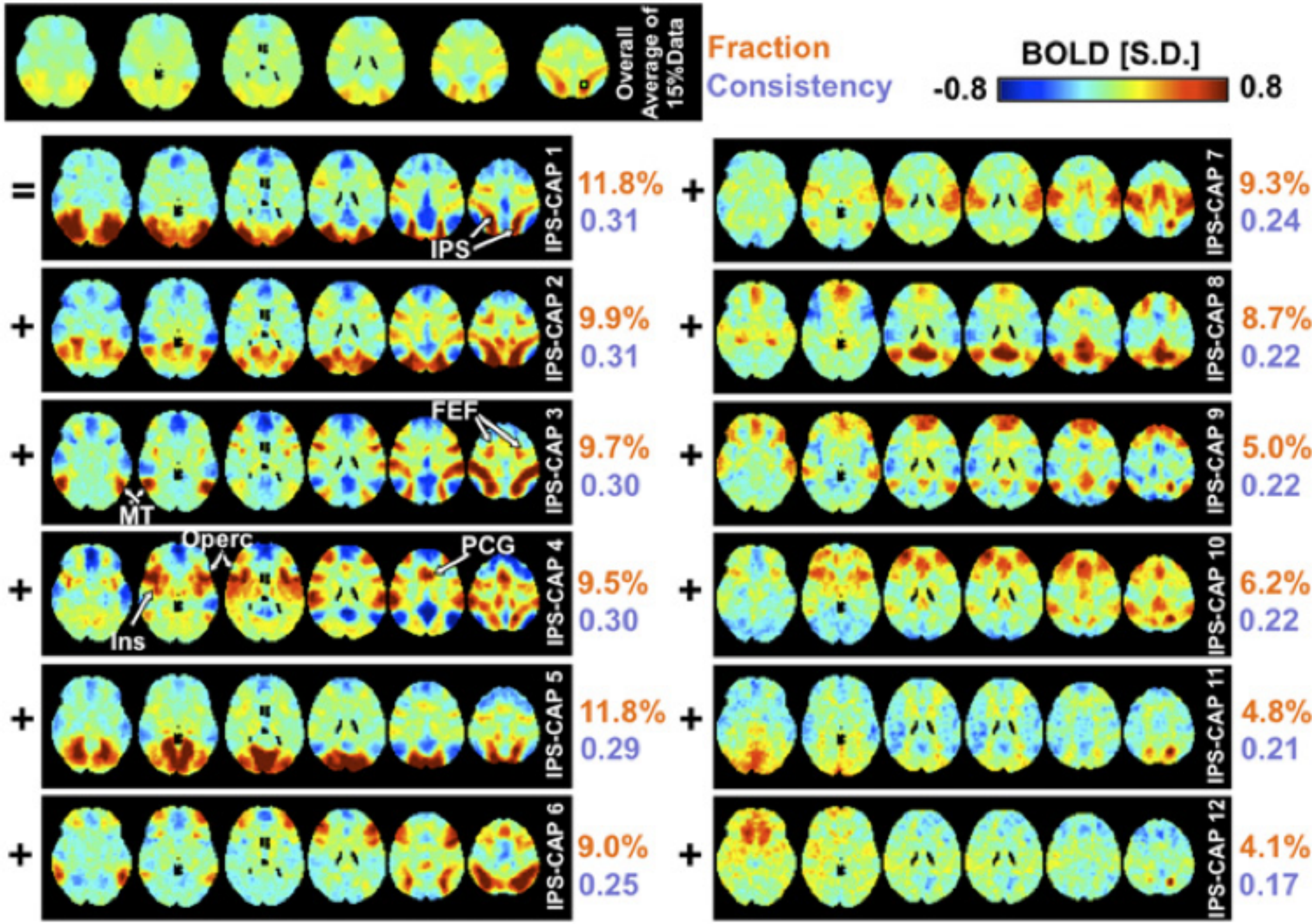
Identical network patterns to those found via static FC can be obtained by averaging spatial maps of frames with strong signal.

Tagliazucchi E et al. (2010); Lui et Dyun (2013) PNAS; Chen et al. (2015) NeuroImage

ASSUMPTION: All dynamics of interest are captured by a limited number of sparse, strong and short (1TR) events



Tagliazucchi E et al. (2010); Lui et Dyun (2013) PNAS; Chen et al. (2015) NeuroImage



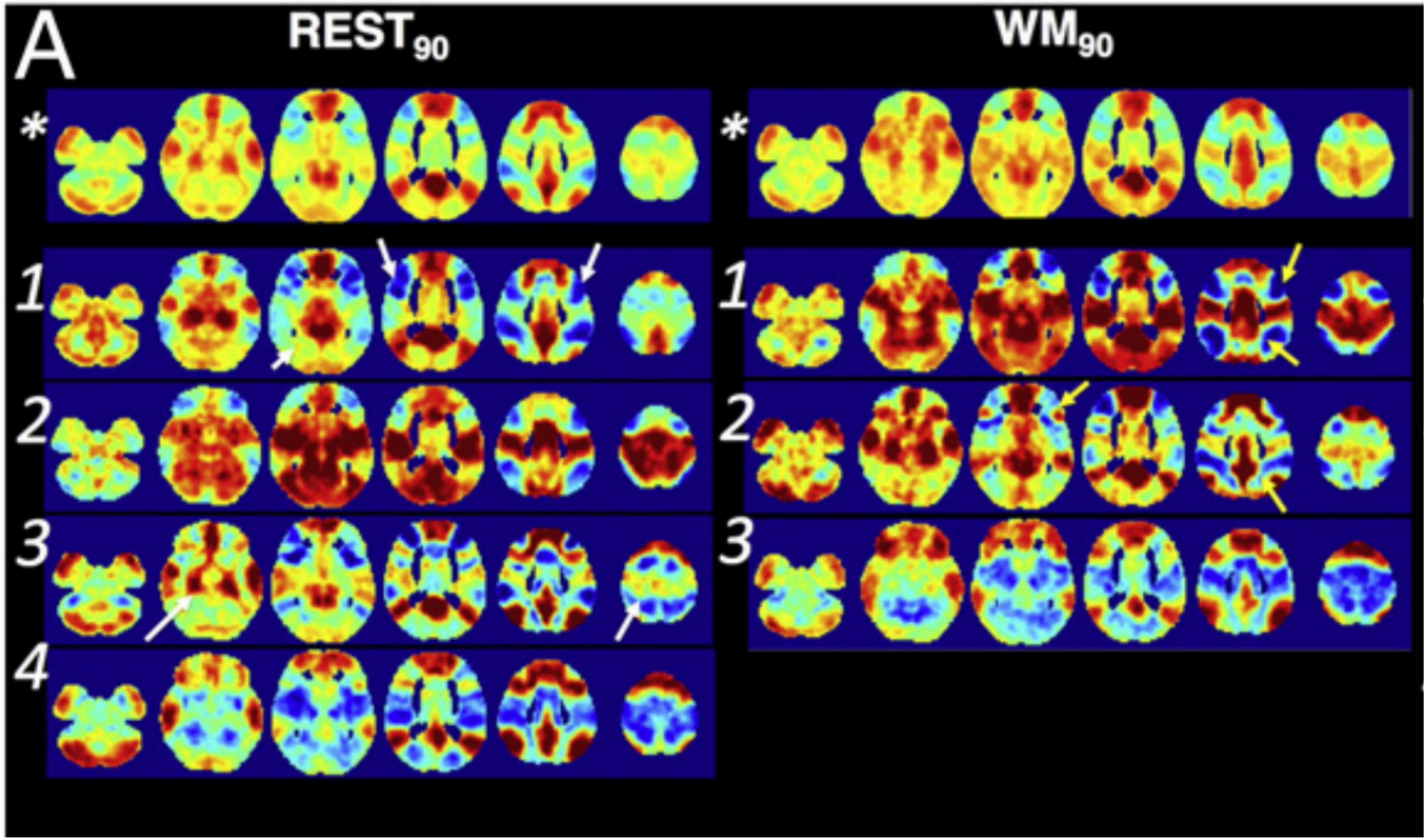
Example: Decomposition of the Dorsal Attention Network in 12 CAPS (seed in IPS)

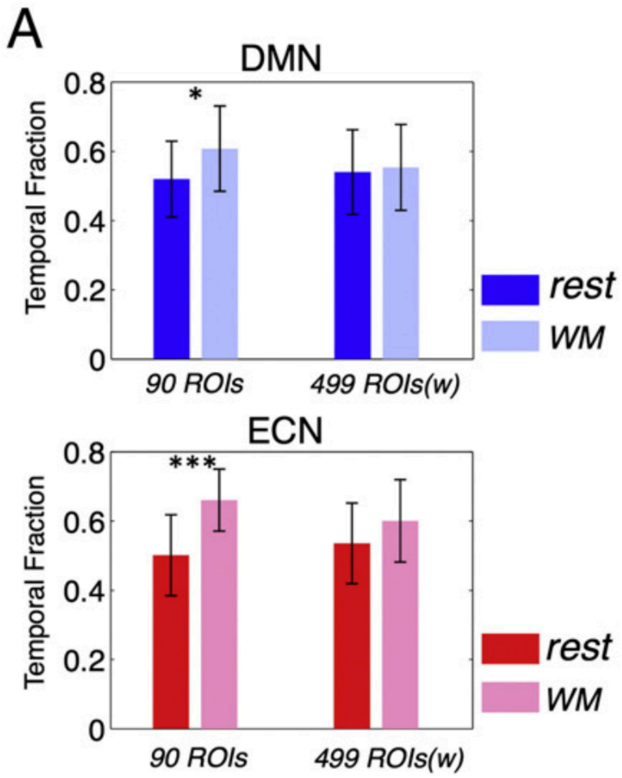
Lui et Dyun, PNAS, 2013

CAPs Derivatives:

- Number of CAPs: Reflects the diversity of network patterns (more CAPs, more patterns)
- Consistency across CAPs: uniformity of brain dynamics (higher consistency, less likely to have extreme dynamics)
- CAP Temporal Fraction: how long it occupies (higher TFs, less dynamics)
- Frequency of state alterations in CAPs: (higher frequency, more dynamics)

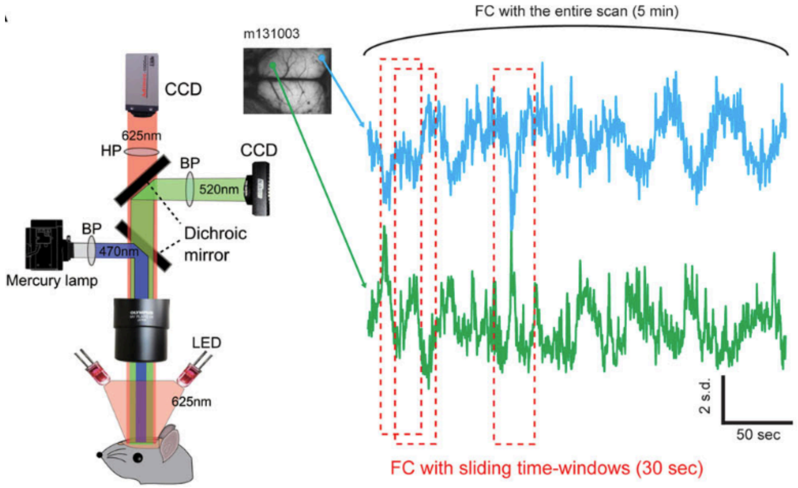
Differences between Rest and Working Memory Task

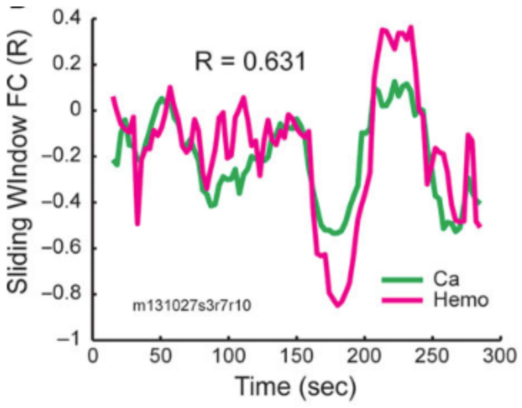


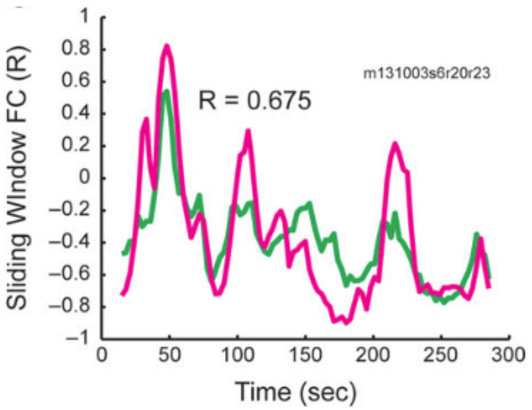


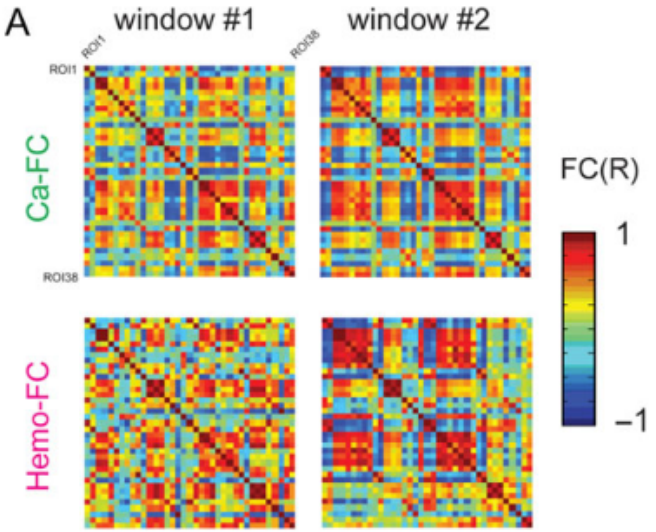
Chen et al. (2015) NeuroImage

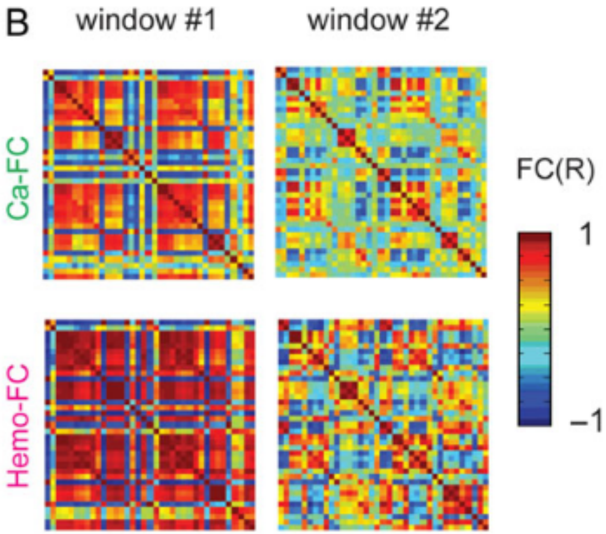
Relationship between Hemodynamic and Neuronal FC Dynamics









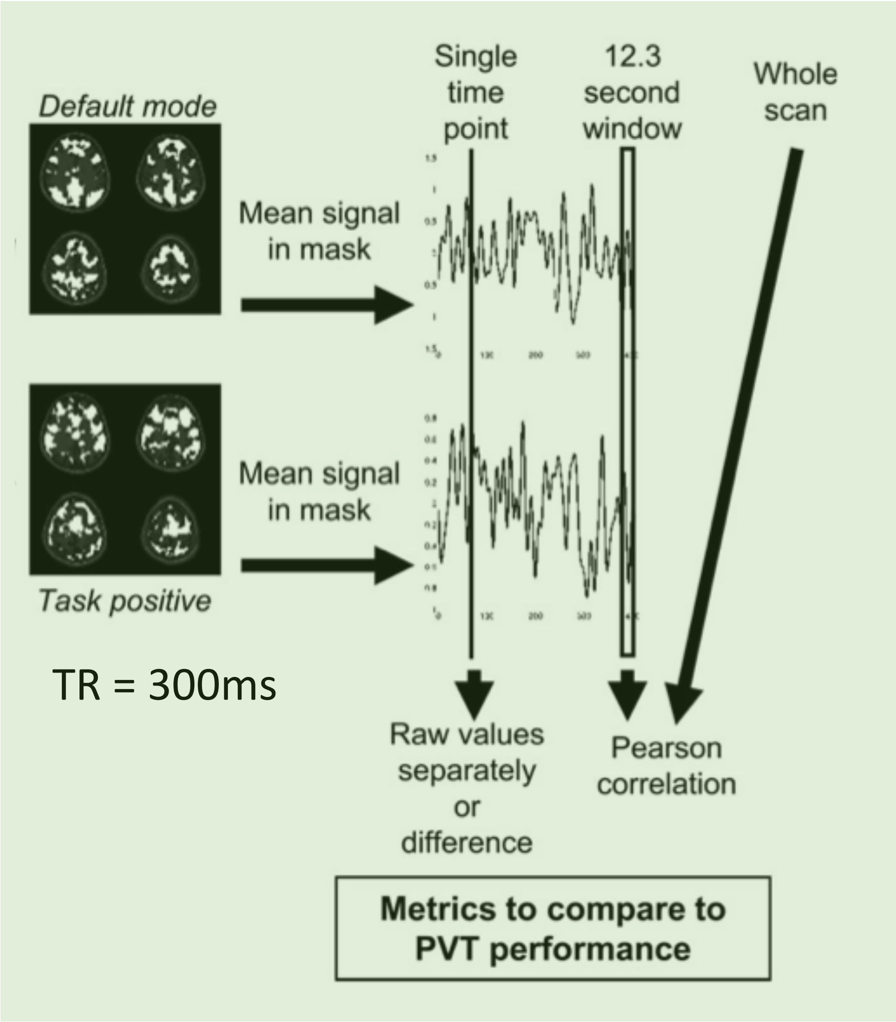


"Together these results suggest that temporal variability in hemodynamic FC, as measured with a sliding window, arises from neural activity rather than from movement-related artifacts (Laumann et al. 2016) or non-neuronal physiological artifacts such as heartbeat and respiration (Bianciardi et al. 2009; Shmueli et al. 2007)"

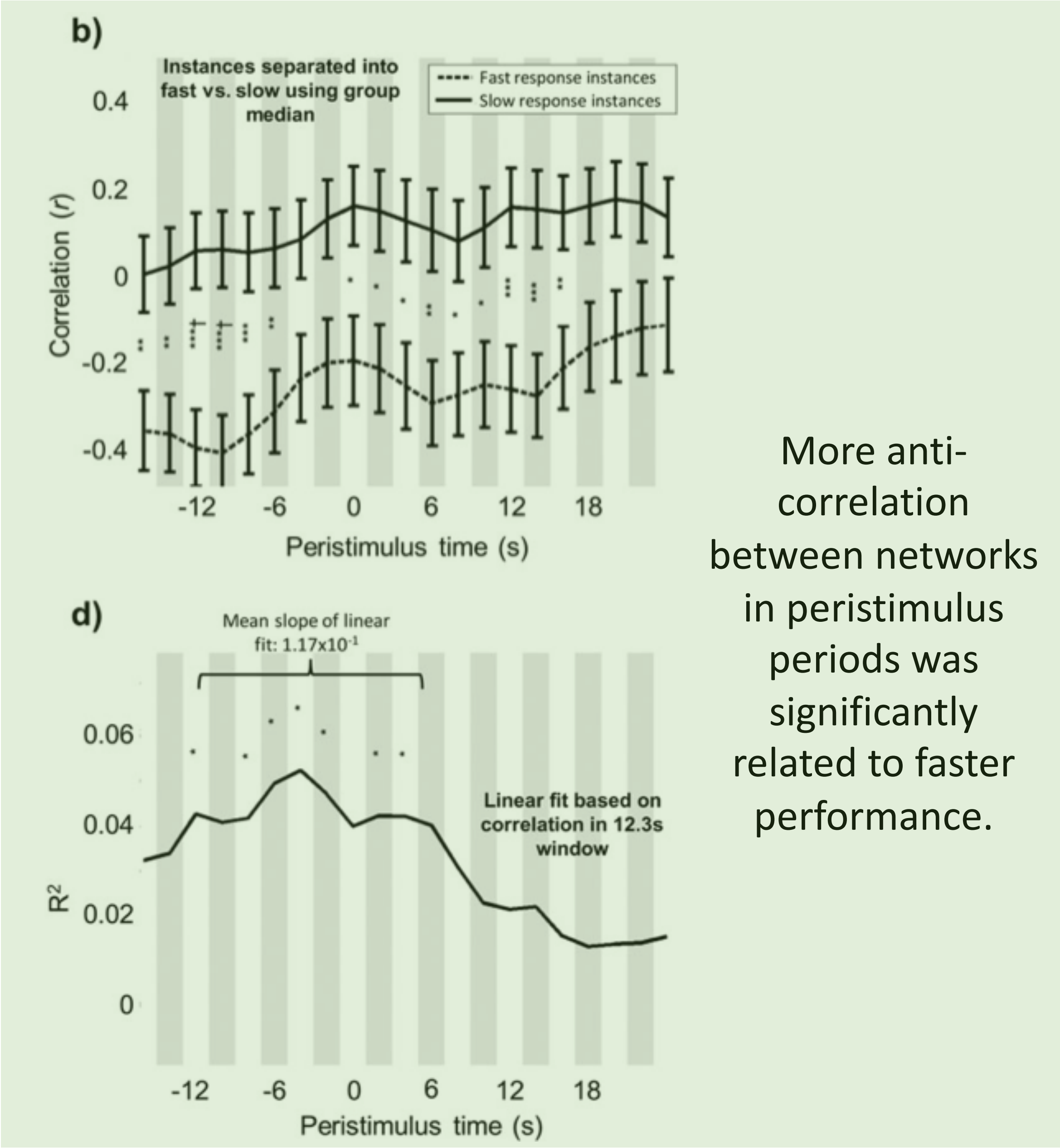
Matsui et al. (2019), Cerebral Cortex

IS IT MEANINGFUL?

Dynamic FC can help predict the outcome of upcoming task trials



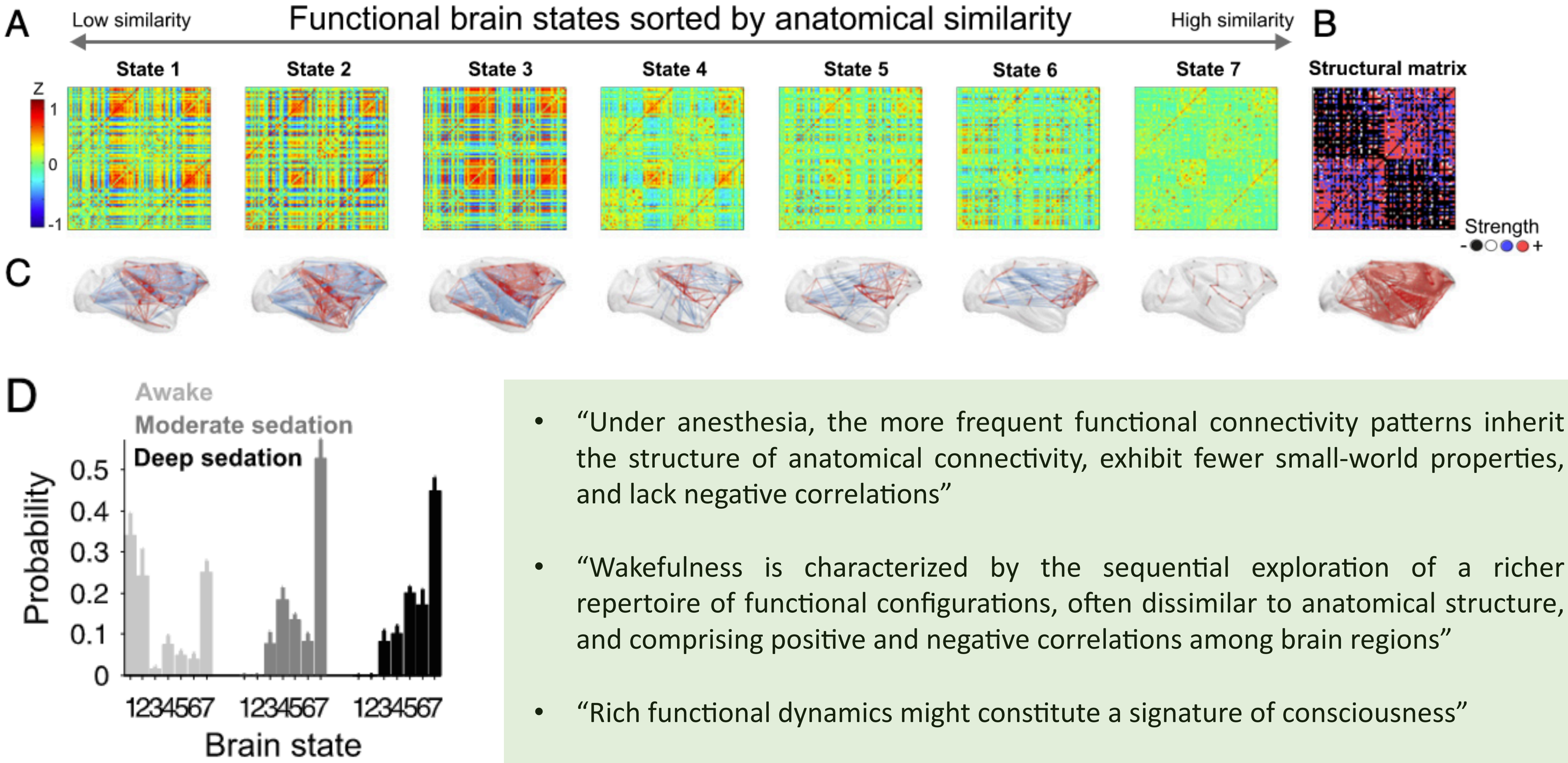
TR = 300ms



More anti-correlation between networks in peristimulus periods was significantly related to faster performance.

Thompson et al. Human Brain Mapping 2013

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)

IS IT MEANINGFUL?

Dynamic FC can predict many task-based phenotypes

- Resting dFC in 747 participants
- 58 Phenotypic Measures: cognitive, emotional, social and personality traits

	HCP Field	Friendly Name	Class		HCP Field	Friendly Name	Class
1.	PicSeq Unadj	Visual Episodic Memory	TA	30.	WM Task Acc	Working Memory (N-back)	TA
2.	CardSort Unadj	Cognitive Flexibility	TA	31.	NEOFAC A	Agreeableness (NEO)	SR
3.	Flanker Unadj	Inhibition (Flanker Task)	TA	32.	NEOFAC O	Openness (NEO)	SR
4.	PMAT24 A CR	Fluid Intelligence	TA	33.	NEOFAC C	Conscientiousness (NEO)	SR
5.	ReadEng Unadj	Vocabulary (Pronunciation)	TA	34.	NEOFAC N	Neuroticism (NEO)	SR
6.	PicVocab Unadj	Vocabulary (Picture Matching)	TA	35.	NEOFAC E	Extroversion (NEO)	SR
7.	ProcSpeed Unadj	Processing Speed	TA	36.	ER40 CR	Emotion Recog. – Total	TA
8.	DDisc AUC 40K	Delay Discounting	UC	37.	ER40ANG	Emotion Recog. – Anger	TA
9.	VSPLOT TC	Spatial Orientation	TA	38.	ER40FEAR	Emotion Recog. – Fear	TA
10.	SCPT SEN	Sustained Attention – Sens.	TA	39.	ER40HAP	Emotion Recog. – Happiness	TA
11.	SCPT SPEC	Sustained Attention – Spec.	TA	40.	ER40NOE	Emotion Recog. – Neutral	TA
12.	IWRD TOT	Verbal Episodic Memory	TA	41.	ER40SAD	Emotion Recog. – Sadness	TA
13.	ListSort Unadj	Working Memory (List Sorting)	TA	42.	AngAffect Unadj	Anger - Affect	SR
14.	MMSE Score	Cognitive Status (MMSE)	TA	43.	AngHostil Unadj	Anger - Hostility	SR
15.	PSQI Score	Sleep Quality	SR	44.	AngAggr Unadj	Anger - Aggressiveness	SR
16.	Endurance Unadj	Walking Endurance	UC	45.	FearAffect Unadj	Fear - Affect	SR
17.	GaitSpeed Comp	Walking Speed	UC	46.	FearSomat Unadj	Fear - Somatic Arousal	SR
18.	Dexterity Unadj	Dexterity	TA	47.	Sadness Unadj	Sadness	SR
19.	Strength Unadj	Grip Strength	UC	48.	LifeSatisf Unadj	Life Satisfaction	SR
20.	Odor Unadj	Odor Identification	UC	49.	MeanPurp Unadj	Meaning of Life	SR
21.	PainInterf Tscore	Pain Interference Survey	SR	50.	PosAffect Unadj	Positive Affect	SR
22.	Taste Unadj	Taste Intensity	UC	51.	Friendship Unadj	Friendship	SR
23.	Mars Final	Contrast Sensitivity	UC	52.	Loneliness Unadj	Loneliness	SR
24.	Emotion Task Face Acc	Emotion Face Matching	TA	53.	PercHostil Unadj	Perceived Hostility	SR
25.	Lang. Task Math Av Diff	Arithmetic	TA	54.	PercReject Unadj	Perceived Rejection	SR
26.	Lang. Task Story Av Diff	Story Comprehension	TA	55.	EmotSupp Unadj	Emotional Support	SR
27.	Relational Task Acc	Relational Processing	TA	56.	InstruSupp Unadj	Instrumental Support	SR
28.	Social Task Perc Rand	Social Cognition – Random	TA	57.	PercStress Unadj	Perceived Stress	SR
29.	Social Task Perc TOM	Social Cognition – Interaction	TA	58.	SelfEff Unadj	Self-Efficacy	SR

Table 2: List of the 58 behavioral measures from the Human Connectome Project used in the present work. These measures were selected so as to span cognitive, emotion and social behavioral aspects and were classified as task performance measures (TA), self-reported measures (SR), or left unclassified (UC).

TA = Task-Performance Measures

Evaluate cognitive processes engaged at timescales on the order of a few seconds.

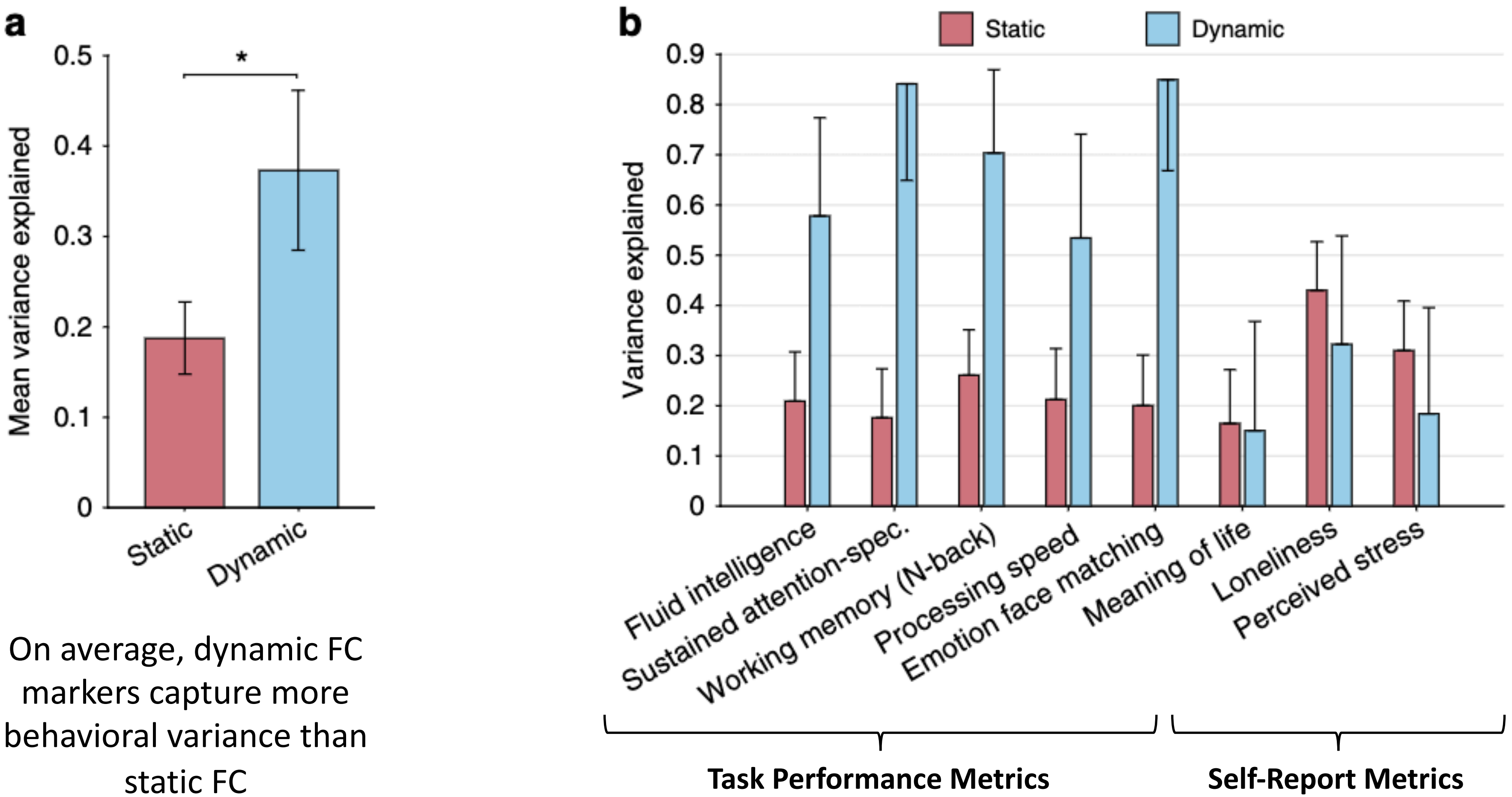
SR = Self-Reported Measures

Reflect trait-like properties that are less likely to change over a few seconds.

Liegeois R. et al. (2019), Nature Communications

Dynamic FC can predict many task-based phenotypes

- Resting dFC in 747 participants
- 58 Phenotypic Measures: cognitive, emotional, social and personality traits

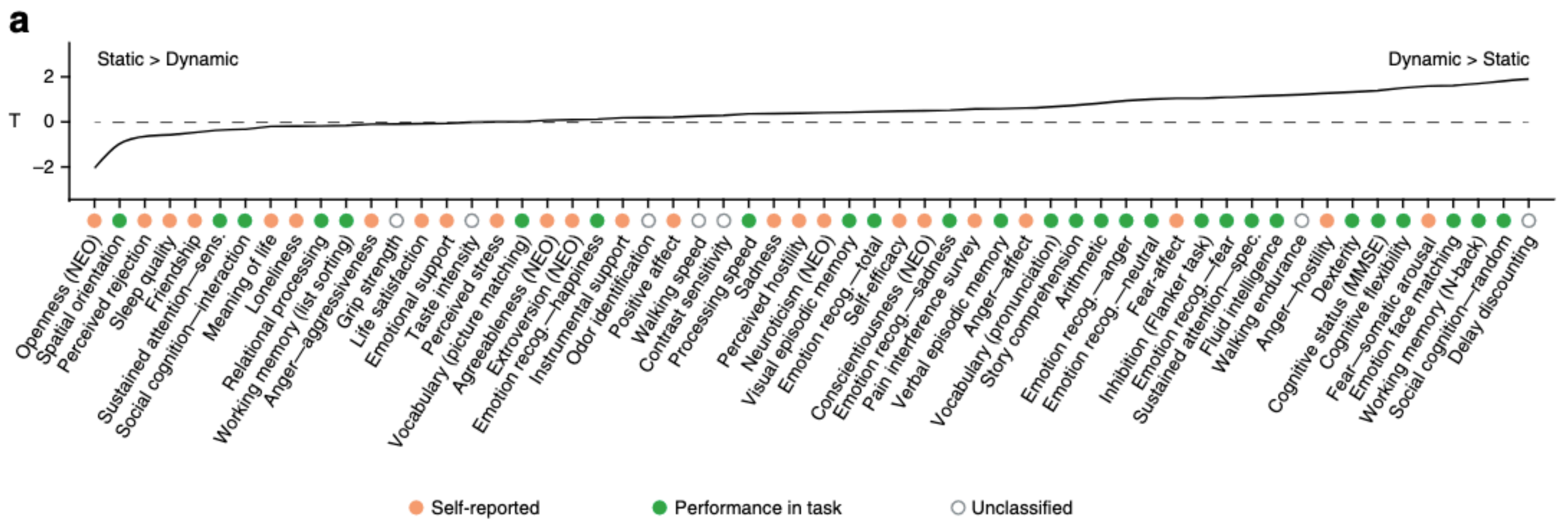


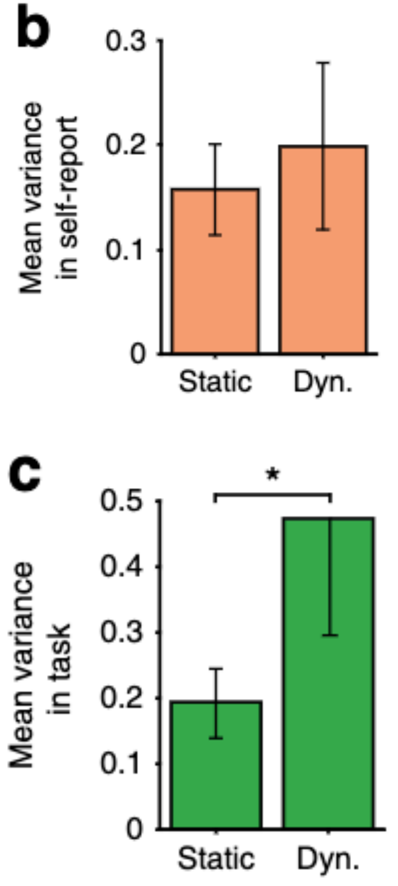
On average, dynamic FC markers capture more behavioral variance than static FC

Liegeois R. et al. (2019), Nature Communications

<u>Dynamic FC can predict many task-based phenotypes</u>

- Resting dFC in 747 participants
- 58 Phenotypic Measures: cognitive, emotional, social and personality traits

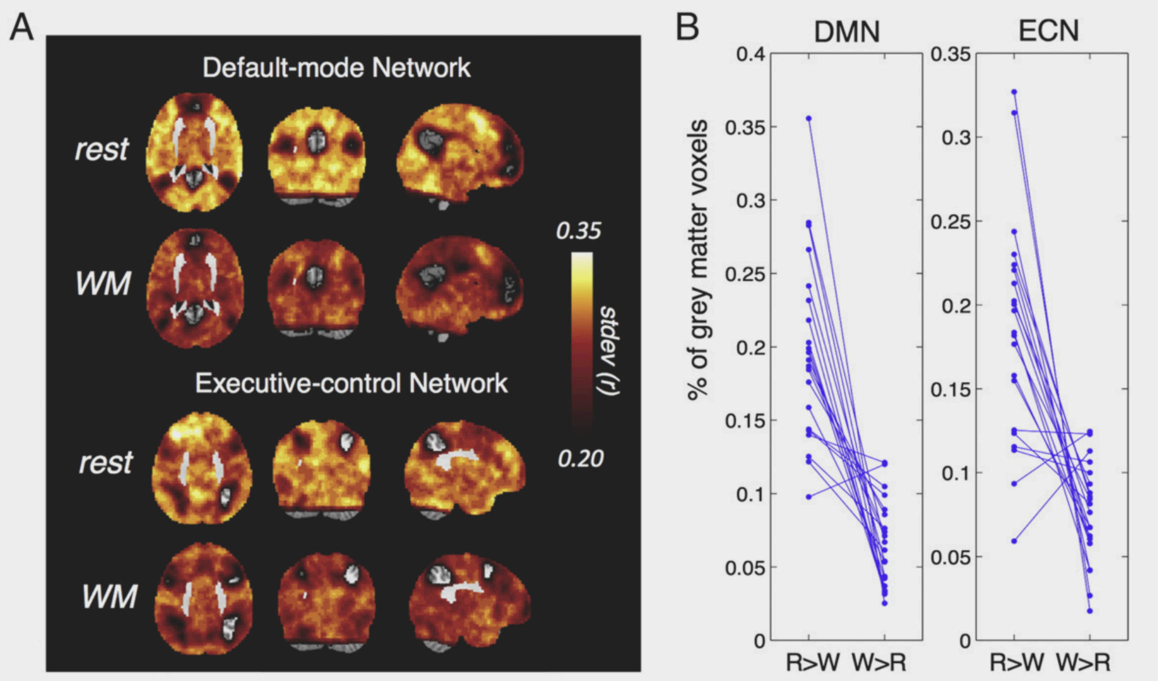




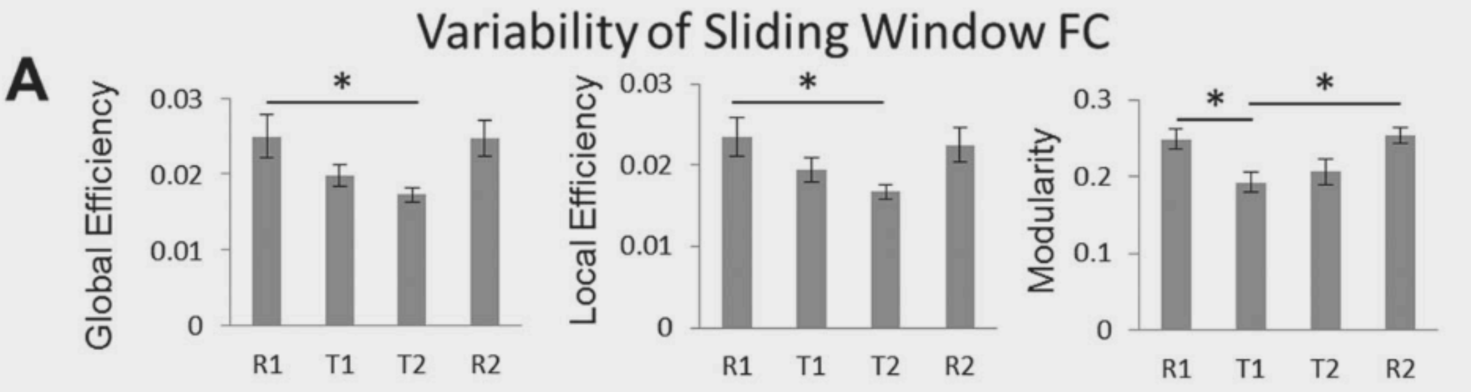
> “Dynamic FC captures task-based phenotypes (e.g., processing speed or fluid intelligence scores), whereas self-reported measures (e.g., loneliness or life satisfaction) are equally well explained by static and dynamic”

Liegeois R. et al. (2019), Nature Communications

Task Engagement is commonly associated with less variable dynamics



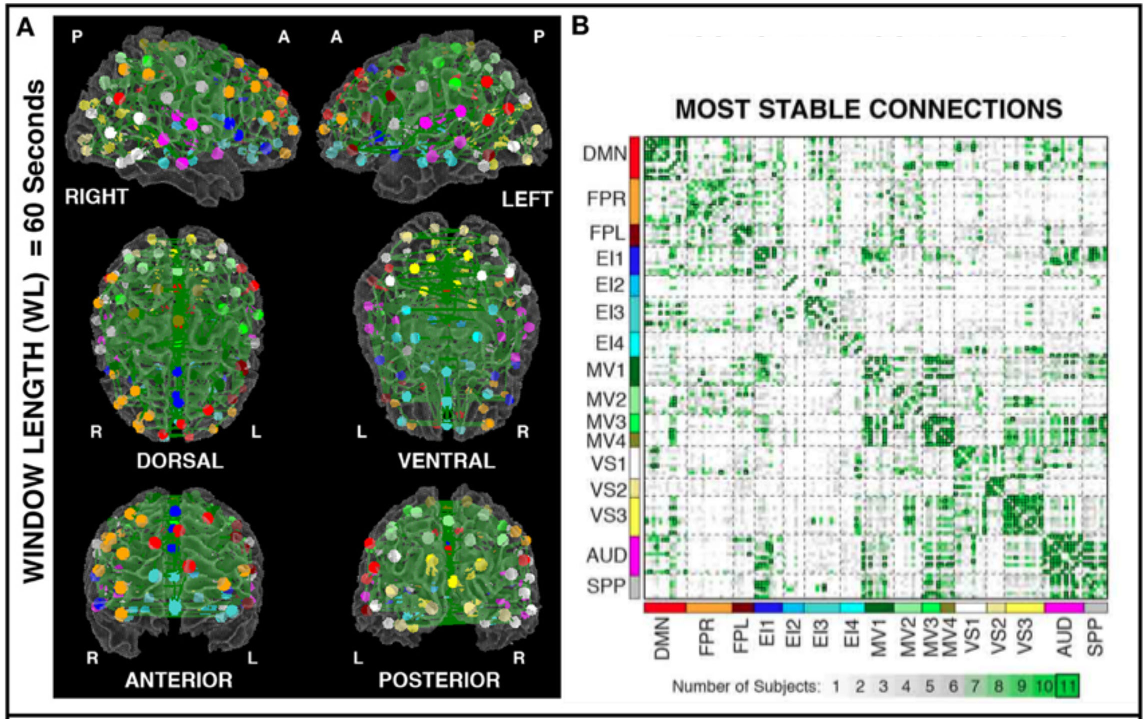
Chen et al. (2015) NeuroImage

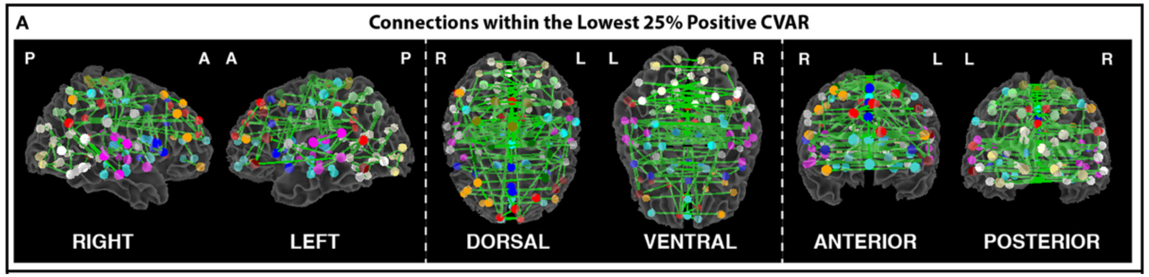


Elton et Gao (2015) Human Brain Mapping

ADDITIONAL OBSERVATIONS

Dynamic FC is spatially organized – Most Stable Connections (I)



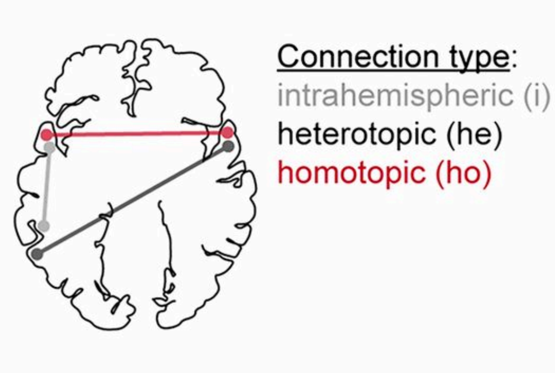


Most stable Connections correspond primarily to symmetric, inter-hemispheric connections between homologous right/left regions. In particular, they correspond to connections among unimodal sensory-motor networks (VIS, AUD and MV).

Gonzalez-Castillo et al., (2104) Frontiers in Neuroscience

ADDITIONAL OBSERVATIONS

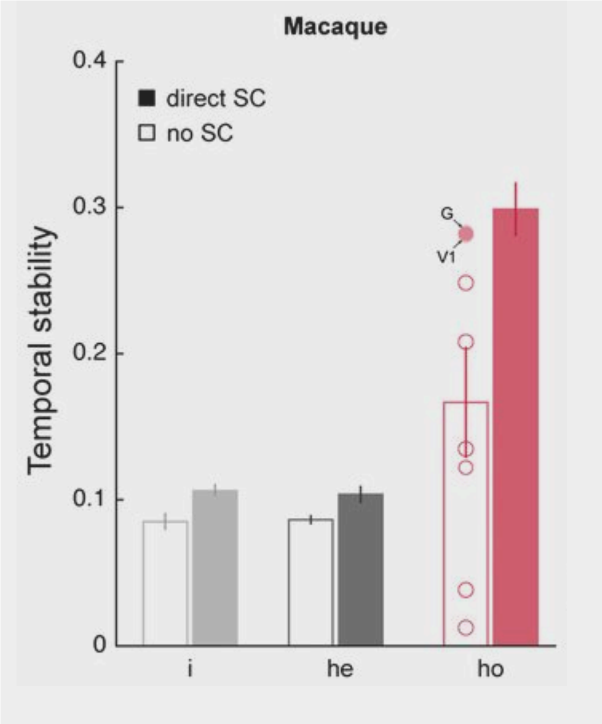
Dynamic FC is spatially organized – Most Stable Connections (II)



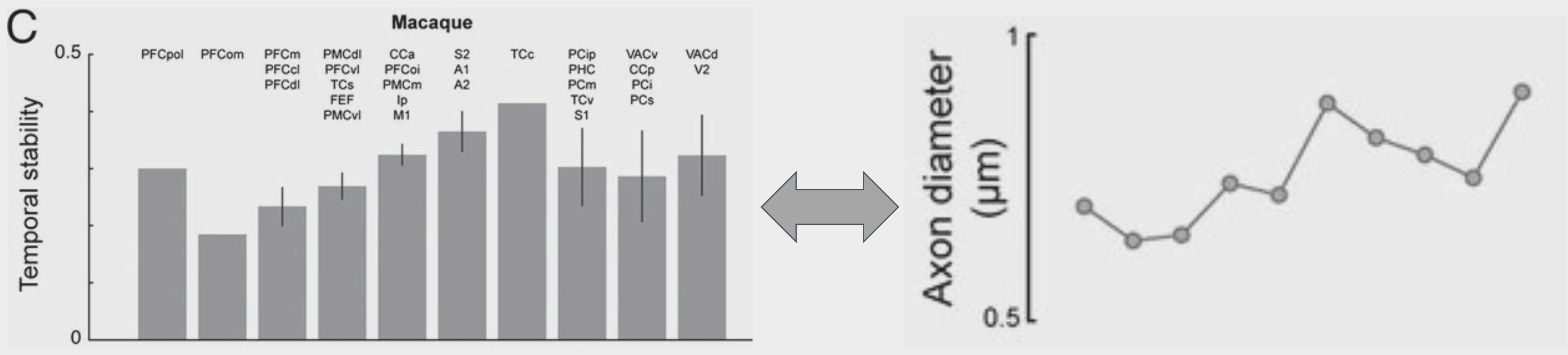
Ho: Interhemispheric connections between homologous ROIs

He: Interhemispheric connections between non-homologous ROIs

I: Intrahemispheric connections.



Compared the profile of temporal stability for homotopic connections with direct structural connectivity properties



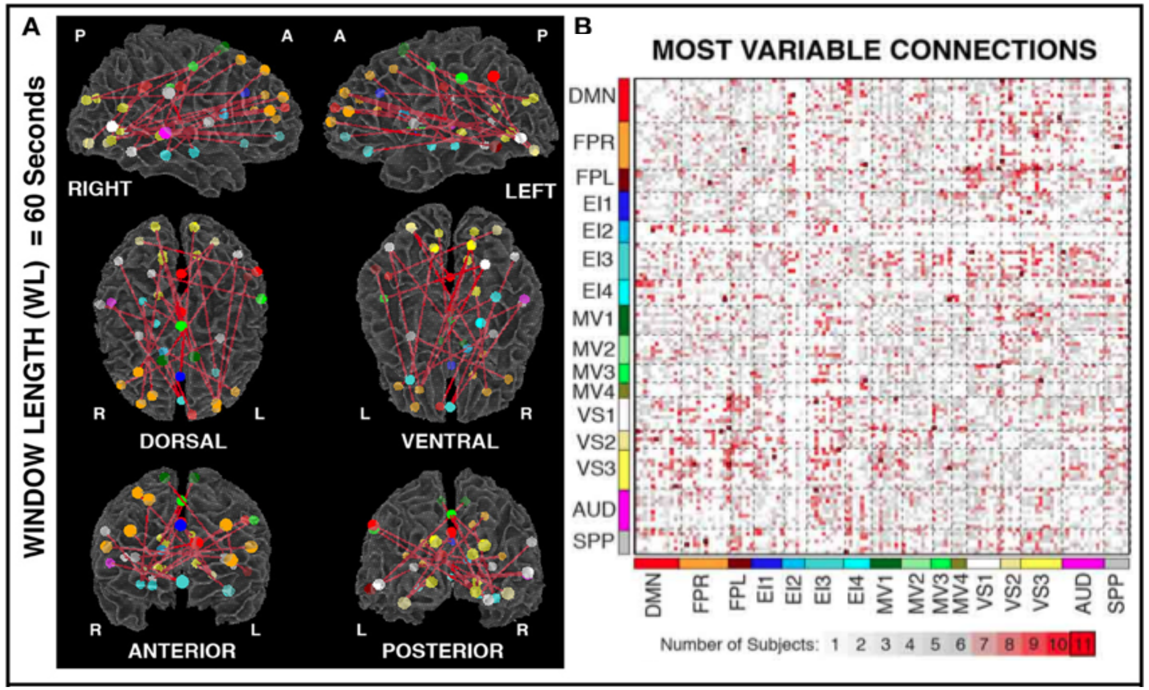
Anterior ←→Posterior

Anterior ←→Posterior

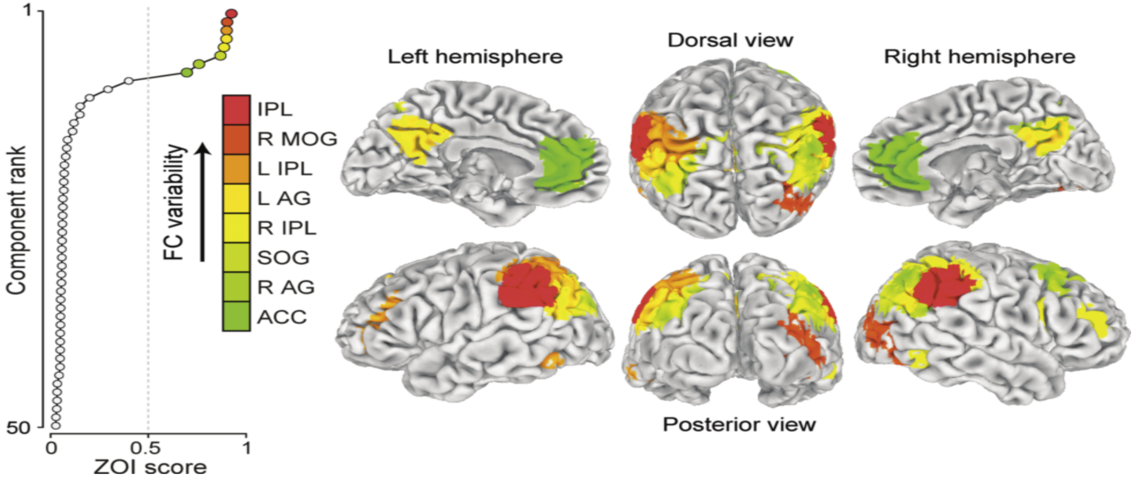
Temporal stability of homotopic FC is facilitated by direct anatomical projections and their conduction characteristics

Shen et al. PNAS 2015

Dynamic FC is spatially organized – Most Variable Connections



Gonzalez-Castillo et al., (2014) Frontiers in Neuroscience

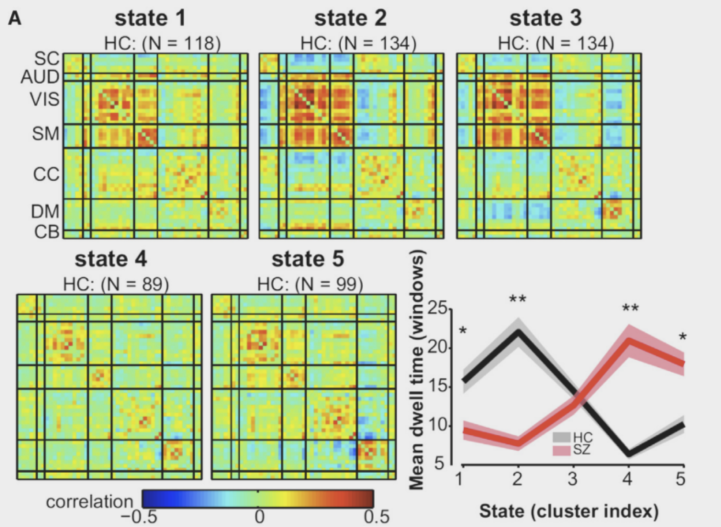


Allen et al. Cerebral Cortex 2014

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

ADDITIONAL OBSERVATIONS

FC Dynamics has potential as a biomarker of disease

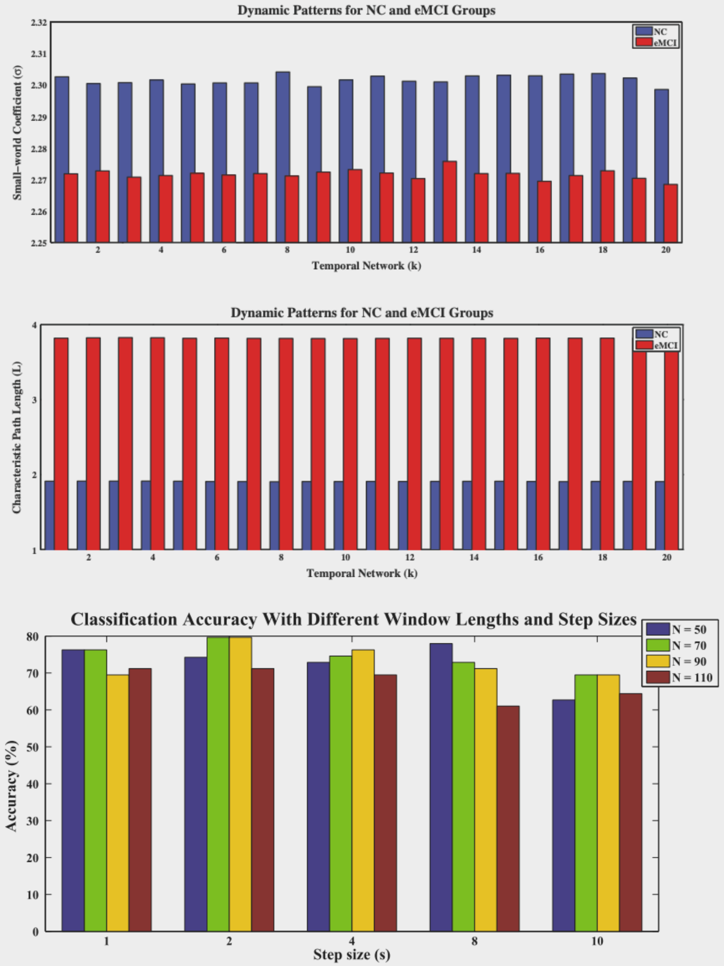


Schizophrenia

Damaraju et al. NeuroImage Clinical, 2014

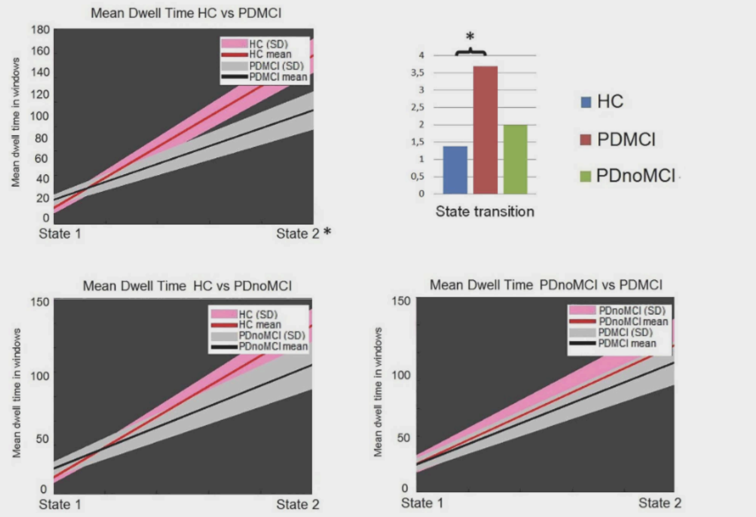
Autism

De Lacy et al. NeuroImage Clinical, 2017



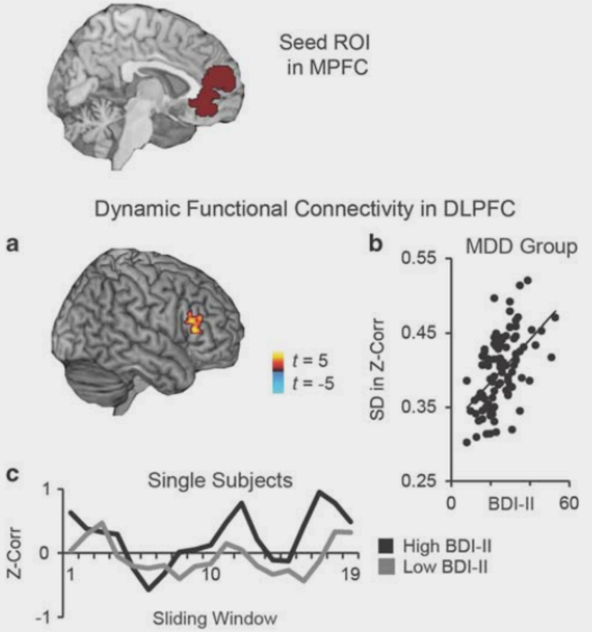
Mild Cognitive Impairment

Wee et al. Brain Imaging and Behavior, 2016



Parkinson's Disease

Diez-Cicarda et al. NeuroImage Clinical, 2017



Depression

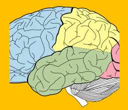
Kaiser et al. Neuropsychopharmacology, 2016

Learned Lessons from Exploring Dynamic FC

RELATIONSHIP BETWEEN HEMODYNAMIC AND NEURONAL DYNAMIC FC

Open Questions / Controversies

Optimal pre-processing



Optimal parcellation scheme

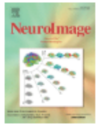
Where to go next…

On the nature of time-varying functional connectivity in resting fMRI

Daniel J. Lurie*[1], Daniel Kessler*[2], Danielle S. Bassett[3,4,5,6], Richard F. Betzel[3], Michael Breakspear[7,8], Shella Keilholz[9], Aaron Kucyi[10], Raphaël Liégeois[11,12], Martin A. Lindquist[13], Anthony Randal McIntosh[14,15], Russell A. Poldrack[16], James M. Shine[17], William Hedley Thompson[16,18], Natalia Z. Bielczyk[19], Linda Douw[20], Dominik Kraft[21], Robyn L. Miller[22], Muthuraman Muthuraman[23], Lorenzo Pasquini[24], Adeel Razi[25,26,27], Diego Vidaurre[28], Hua Xie[29], Vince D. Calhoun*[22,30,31]

https://doi.org/10.31234/osf.io/xtzre

NeuroImage
Volume 180, Part B, 15 October 2018, Pages 526-533



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

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

NeuroImage
Volume 160, 15 October 2017, Pages 41-54

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]

NeuroImage
Volume 80, 15 October 2013, Pages 360-378

Dynamic functional connectivity: Promise, issues, and interpretations

R. Matthew Hutchison[a, 1], Thilo Womelsdorf[b], Elena A. Allen[c, d], Peter A. Bandettini[e], Vince D. Calhoun[d, f], Maurizio Corbetta[g, h], Stefania Della Penna[g], Jeff H. Duyn[i], Gary H. Glover[j], Javier Gonzalez-Castillo[e], Daniel A. Handwerker[e], Shella Keilholz[k], Vesa Kiviniemi[l], David A. Leopold[m], Francesco de Pasquale[g], Olaf Sporns[n], Martin Walter[o, p], Catie Chang[i, 1]

NeuroImage
Volume 188, March 2019, Pages 502-514

Efficacy of different dynamic functional connectivity methods to capture cognitively relevant information

Hua Xie[a, b], Charles Y. Zheng[c], Daniel A. Handwerker[b], Peter A. Bandettini[b, d], Vince D. Calhoun[e, f], Sunanda Mitra[a], Javier Gonzalez-Castillo[b]

NeuroImage
Volume 163, December 2017, Pages 437-455

Interpreting temporal fluctuations in resting-state functional connectivity MRI

Raphaël Liégeois[a], Timothy O. Laumann[b], Abraham Z. Snyder[b, c], Juan Zhou[d], B.T. Thomas Yeo[a, d, e]