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

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August 29th, NIMH Summer fMRI Course
Main Questions we will try 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)

Brain Parcellation

ROI Timeseries

Scan Session (5 – 10 mins)

Functional Connectivity Matrix

Pearson’s R

B

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

Gratton et al., Neuron (2018)
WHAT IS IT?

Brain Parcellation

Scan Session (5 – 10 mins)

ROI Timeseries

Pearson's R

0 – 60s

30 – 90s

60 – 120s

300 – 360s

B

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

Gratton et al., Neuron (2018)
WHAT IS IT?

Many FC Matrix per Scan

One dynamic FC Matrix per Scan
WHAT IS IT?

**Dynamic Functional Connectivity (DFC)**
- Many FC Matrix per Scan
- Changes with brain states (minutes)
- Circadian/ slow changes (hours, days)

**Static Functional Connectivity (SFC)**
- One static FC per Scan
- Stable across people
- Stable in an individual

**Diagram:**
- **Dynamic Functional Connectivity**
  - Time [as windows]
  - Connections

- **Static Functional Connectivity**
  - ROIs

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**Experiences Represented:**
- Moment-to-moment variation (seconds)
- Changes with brain states (minutes)
- Circadian/ slow changes (hours, days)
- Changes with extensive experience (weeks, years)
**WHAT IS IT?**

**TIME-VARYING AT SHORT TEMPORAL SCALE**
- One FC configuration per scan
- Invariant to temporal re-ordering of time points (memoryless)
- Summary statistics are not time dependent

**SYSTEMS THEORY**
- Summary statistics are not time dependent

**STATISTICS**
- Summary statistics are not time dependent

**STATIC FUNCTIONAL CONNECTIVITY**

**DYNAMIC FUNCTIONAL CONNECTIVITY**
- Several FC configurations per scan
- Non-Invariant to temporal re-ordering of time points (memory)
- Summary statistics are time dependent

**Sliding Windows**
- Brain States
- CAPs
- QPPs

**Autocorrelation Models**

**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

**Time-varying Graph Theory Metrics**
- Dynamic Conditional Correlation
- Co-Activation Patterns
- All pairwise combinations
- Dynamic graph analysis

**Point-Process / Deconvolution**
- Wavelets / Time-Freq. Analyses
- Quasi-Periodic Patterns
- Time-varying Graph Theory Metrics

**Observation of events**
- Frame-wise analysis

**Co-Activity Patterns**
- Extracting dFC states
- Dynamic graph analysis

**Temporal modeling**
- Hidden Markov Models
- Multi-Layer Networks

**State modeling**
- Clustering (k-means)
ASSUMPTION: FC Dynamics is appropriately modeled as a succession of a finite number of discrete FC configurations with sharp transitions between them.

How to choose k?
Similarity Metric?
Clustering Algorithm?

Summary Statistics (e.g., dwell times, number of transitions, trajectories)
HOW TO MEASURE IT?

FC State Models

STATIC FC MATRIX

State 1 (33%)
- sub-cortical
- auditory
- somatomotor
- visual
- cognitive control
- default-mode
- cerebellar

Occurrence (%)
- 45
- 35
- 25
- 15
- 5
- 0

Time (s)
- 50
- 100
- 150
- 200
- 250

State 2 (7%)

State 3 (0%)

State 4 (12%)
- sub-cortical
- auditory
- somatomotor
- visual
- cognitive control
- default-mode
- cerebellar

Occurrence (%)
- 15
- 10
- 5
- 0

Time (s)
- 50
- 100
- 150
- 200
- 250

State 5 (14%)

State 6 (10%)

State 7 (15%)

Allen et al. Cer. Cortex, 2014
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
“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]”


Additional References on Null Models Discussion
HOW TO MEASURE IT?

FC State Models

Mental States Imposed by Experiment

Atlas Time Series Extraction

Dimensionality Reduction (PCA)

Time Segmentation

Computation of Windowed FC Patterns

K-MEANS: Only FC patterns enter the algorithm. No information about mental tasks or the temporal ordering of the FC Patterns is provided.

FC State Detection

FC State Timeline

Validation

Comparison between FC and mental state timelines via Adjusted Rand Index and visualization

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?

Exemplar Top Eigenconnectivities for 1 subject

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**
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)
Dynamic FC can help predict the outcome of upcoming task trials

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”
Dynamic FC can predict many task-based phenotypes

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

<table>
<thead>
<tr>
<th>HCP Field</th>
<th>Friendly Name</th>
<th>Class</th>
<th>HCP Field</th>
<th>Friendly Name</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PicSeq Unadj</td>
<td>Visual Episodic Memory</td>
<td>TA</td>
<td>30. WM Task Acc</td>
<td>Working Memory (N-back)</td>
<td>TA</td>
</tr>
<tr>
<td>2. CardSort Unadj</td>
<td>Cognitive Flexibility</td>
<td>TA</td>
<td>31. NEOFAC A</td>
<td>Agreeableness (NEO)</td>
<td>SR</td>
</tr>
<tr>
<td>3. Flanker Unadj</td>
<td>Inhibition (Flanker Task)</td>
<td>TA</td>
<td>32. NEOFAC O</td>
<td>Openness (NEO)</td>
<td>SR</td>
</tr>
<tr>
<td>4. PMAT24 A CR</td>
<td>Fluid Intelligence</td>
<td>TA</td>
<td>33. NEOFAC C</td>
<td>Conscientiousness (NEO)</td>
<td>SR</td>
</tr>
<tr>
<td>5. Reading Unadj</td>
<td>Vocabulary ( Pronunciation)</td>
<td>TA</td>
<td>34. NEOFAC N</td>
<td>Neuroticism (NEO)</td>
<td>SR</td>
</tr>
<tr>
<td>6. PoVocab Unadj</td>
<td>Vocabulary (Picture Matching)</td>
<td>TA</td>
<td>35. NEOFAC E</td>
<td>Extraversion (NEO)</td>
<td>SR</td>
</tr>
<tr>
<td>7. ProcSpeed Unadj</td>
<td>Processing Speed</td>
<td>TA</td>
<td>36. ER40 CR</td>
<td>Emotion Recog. – Total</td>
<td>TA</td>
</tr>
<tr>
<td>8. DDac AUC 40K</td>
<td>Delay Discounting</td>
<td>UC</td>
<td>37. ER40ANG</td>
<td>Emotion Recog. – Anger</td>
<td>TA</td>
</tr>
<tr>
<td>9. VSPLOT TC</td>
<td>Spatial Orientation</td>
<td>TA</td>
<td>38. ER40FEAR</td>
<td>Emotion Recog. – Fear</td>
<td>TA</td>
</tr>
<tr>
<td>10. SCPT SEN</td>
<td>Sustained Attention – Sens.</td>
<td>TA</td>
<td>39. ER40HAP</td>
<td>Emotion Recog. – Happiness</td>
<td>TA</td>
</tr>
<tr>
<td>11. SCPT SPEC</td>
<td>Sustained Attention – Spec.</td>
<td>TA</td>
<td>40. ER40NE</td>
<td>Emotion Recog. – Neutral</td>
<td>TA</td>
</tr>
<tr>
<td>12. IWRD TOT</td>
<td>Verbal Episodic Memory</td>
<td>TA</td>
<td>41. ER40AD</td>
<td>Emotion Recog. – Sadness</td>
<td>TA</td>
</tr>
<tr>
<td>13. ListSort Unadj</td>
<td>Working Memory (List Sorting)</td>
<td>TA</td>
<td>42. AngHostil Unadj</td>
<td>Anger - Affect</td>
<td>SR</td>
</tr>
<tr>
<td>14. MMSE Score</td>
<td>Cognitive Status (MMSE)</td>
<td>TA</td>
<td>43. AngHostil Unadj</td>
<td>Anger - hostility</td>
<td>SR</td>
</tr>
<tr>
<td>15. PSQI Score</td>
<td>Sleep Quality</td>
<td>SR</td>
<td>44. AngAngr Unadj</td>
<td>Anger - Aggressiveness</td>
<td>SR</td>
</tr>
<tr>
<td>16. Endurance Unadj</td>
<td>Walking Endurance</td>
<td>UC</td>
<td>45. FearAffect Unadj</td>
<td>Fear - Affect</td>
<td>SR</td>
</tr>
<tr>
<td>17. GaitSpeed Comp</td>
<td>Walking Speed</td>
<td>UC</td>
<td>46. FearSomat Unadj</td>
<td>Fear - Somatic Arousal</td>
<td>SR</td>
</tr>
<tr>
<td>18. Dexterity Unadj</td>
<td>Dexterity</td>
<td>TA</td>
<td>47. Sadness Unadj</td>
<td>Sadness</td>
<td>SR</td>
</tr>
<tr>
<td>20. Odor Unadj</td>
<td>Odor Identification</td>
<td>UC</td>
<td>49. MeanPurp Unadj</td>
<td>Meaning of Life</td>
<td>SR</td>
</tr>
<tr>
<td>22. Taste Unadj</td>
<td>Taste Intensity</td>
<td>UC</td>
<td>51. Friendship Unadj</td>
<td>Friendship</td>
<td>SR</td>
</tr>
<tr>
<td>23. Mars Final</td>
<td>Contrast Sensitivity</td>
<td>UC</td>
<td>52. Loneliness Unadj</td>
<td>Loneliness</td>
<td>SR</td>
</tr>
<tr>
<td>27. Relational Task Acc</td>
<td>Relational Processing</td>
<td>TA</td>
<td>56. InstrSupp Unadj</td>
<td>Instrumental Support</td>
<td>SR</td>
</tr>
</tbody>
</table>

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).

IS IT MEANINGFUL?

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
Dynamic FC can predict many task-based phenotypes

- 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”
Task Engagement is commonly associated with less variable dynamics.

Chen et al. (2015) *NeuroImage*

Elton et Gao (2015) *Human Brain Mapping*
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
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.

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

Most Variable Connections correspond primarily inter-network, inter-hemispheric connections involving the fronto-parietal network and occipital regions. Also some DMN regions.
FC Dynamics has potential as a biomarker of disease

Damaraju et al. NeuroImage Clinical, 2014

Schizophrenia

De Lacy et al. NeuroImage Clinical, 2017

Autism

Wee et al. Brain Imaging and Behavior, 2016

Mild Cognitive Impairment

Kaiser et al. Neuropsychopharmacology, 2016

Depression

Diez-Cicarda et al. NeuroImage Clinical, 2017

Parkinson’s Disease

ADDITIONAL OBSERVATIONS
Learned Lessons from Exploring Dynamic FC

RELATIONSHIP BETWEEN HEMODYNAMIC AND NEURONAL DYNAMIC FC
Open Questions / Controversies

- Optimal pre-processing
- Optimal parcellation scheme
- Working definition of what we all mean by dynamic FC
- Devising appropriate null models to test for the “existence of dynamics”
- What is the etiology of dynamic FC during rest?
- Are dynamics better modelled as discrete or continuous process?
- Convergence of methods to facilitate across-studies comparisons
Where to go next...

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

Daniel J. Lurie 1,2, Daniel Kessler 1,2, Danielle S. Bassett 3,4,5, Richard F. Betzel 2, Michael Breakspear 7,8, Shella Keilholz 2, 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 18,19, Natalia Z. Bielczyk 10, Linda Douw 19, Dominik Kraft 11, Robyn L. Miller 22, Muthuraman Muthuraman 23, Lorenzo Pasquaali 24, Adeeel Razi 15,26,27, Diego Vidalurre 19, Hua Xie 28, Vincent D. Calhoun 22,23,31

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

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

Javier Gonzalez-Castillo 1,2, Peter A. Bandettini 1,2

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

**Dynamic functional connectivity: Promise, issues, and interpretations**

R. Matthew Hutchison 1,2,3,8, Thilo Womelsdorf 3, Elena A. Allen 4,5, Peter A. Bandettini 1, Vince D. Calhoun 1,5,17, Maurizio Corbetta 1,8, Stefania Della Penna 1, Jeff H. Duyn 1, Gary H. Glover 1, Javier Gonzalez-Castillo 1, Daniel A. Harderwerker 1, Shella Keilholz 2, Vesna Kucyi 1, David A. Leopold 1, Francesco de Pasquale 1, Olaf Sporns 4, Martin Walter 1,2, Cate Chang 1,2,3,8

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

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

Hua Xie 28, Charles Y. Zheng 5, Daniel A. Harderwerker 3, Peter A. Bandettini 1,2, Vince D. Calhoun 1,5, Sunanda Mitra 3, Javier Gonzalez-Castillo 1

NeuroImage
Volume 188, March 2019, Pages 502-514

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

Maria Giulia Preti 1,2,3,4, Thomas AW Bolton 1,5,6, Dimitri Van De Ville 1,2

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

**Interpreting temporal fluctuations in resting-state functional connectivity MRI**

Raphaël Liégeois 1,2,3, Timothy O. Laumann 4, Abraham Z. Snyder 5,6,7, Juan Zhou 6, B.T. Thomas Yeo 1,2

NeuroImage
Volume 163, December 2017, Pages 437-455