Functional MRI of the dynamic brain: quasiperiodic patterns, brain states, and trajectories

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20 March 2018
Resting State fMRI
No stimulus
Looks at spontaneous BOLD fluctuations
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“Average” or “Static” Functional Connectivity
Calculated over the course of the entire scan
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“Dynamic” Connectivity
Sliding window correlation
Co-activation patterns or point process analysis
Repeated patterns
Hidden Markov Models
Clustering
Dimensionality reduction
Resting State fMRI
No stimulus
Looks at spontaneous BOLD fluctuations

“Average” or “Static” Functional Connectivity
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Repeated patterns (QPPs)
Hidden Markov Models
Clustering
Dimensionality reduction
Dynamic Connectivity

• Cognitive changes ~ seconds, functional connectivity ~ minutes
• Spontaneous fluctuations hypothesized to reflect neural activity; temporal information may provide insight
• Reasonable to expect that short epochs also linked to neural states
• Short time windows improve sensitivity to schizophrenia\(^1\), predict trial-to-trial performance\(^2\)

BUT...

• Variability in “connectivity” observed for areas that share no temporal information, SWC poor representation of underlying correlation structure\(^3-6\)

\(^1\) Sakoglu et al., MAGMA 2010; \(^2\) Thompson et al., Hum Brain Mapp 2013; \(^3\) Handwerker et al., NeuroImage 2012; \(^4\) Keilholz et al., Brain Connect 2013; \(^5\) Shakil et al, NeuroImage 2016; Hindriks et al., NeuroImage 2015
Quasi-periodic patterns (QPPs)

- First observed during visual inspection of data from anesthetized rodents
- Waves of high and low signal propagate along the cortex from lateral to medial areas
- Developed pattern-finding algorithm that identifies spatiotemporal template of pattern and time course of its strength over the course of the scan
- In humans, involves alternation of DMN and TPN activity

Majeed et al., JMRI 2009, Majeed et al, NeuroImage 2011
Spatiotemporal pattern finding algorithm

Looking at a functional scan over time
Spatiotemporal pattern finding algorithm

Pick a chunk of randomly-selected data
Spatiotemporal pattern finding algorithm

Sliding window correlation of the chunk with the entire scan
Each peak identifies a repeated occurrence in the scan.
Spatiotemporal pattern finding algorithm

Select chunks from each of the locations of the peaks
Spatiotemporal pattern finding algorithm

All these chunks should be similar to each other
Spatiotemporal pattern finding algorithm

They are then averaged together
Spatiotemporal pattern finding algorithm

And sliding window correlation with the functional scan is repeated
This whole process is repeated until the updated template doesn’t change.
Spatiotemporal pattern finding algorithm

Results

Pattern template  Sliding window correlation vector
Quasi-periodic patterns

a. Sagittal view

Majeed et al, NeuroImage 2011
QPPs in HCP Data

Yousefi et al, NeuroImage 2018
Before GS Regression

QPPs from individual subjects fall into two groups, one that exhibits anticorrelation and another that does not

Yousefi et al, NeuroImage 2018
After GS Regression
QPPs from individual subjects fall into a single group that exhibits anticorrelation.

Yousefi et al, NeuroImage 2018
HCP Data – Global signal

After GS Regression
QPPs from individual subjects fall into a single group that exhibits anticorrelation.

Moreover
QPPs were similar in subgroups with high and low levels of motion.
QPP type pre-GSR was influenced by respiratory and cardiac variability, but they do not cause the QPP itself.
No evidence of spatial QPP pattern or different delay times across brain

Billings and Keilholz, Brain Connect 2018
HCP Data – Reproducibility across days

- **Reproducibility across days**

  - Correlation between QPPs for each subject in two days (#465)
    - Median: 0.78
    - p(KS test): 1.4e-88

  - Correlation between QPPs for each pair of subjects and days (#465x464x4)
    - Median: 0.65

*Yousefi et al, NeuroImage 2018*
HCP Data – Whole Brain QPPs
Thalamus leads the pattern
QPPs across species

Mice – Belloy et al, NeuroImage 2018

Rats – Majeed et al, NeuroImage 2011

- Anesthetized rats
- Anesthetized mice
- Anesthetized monkeys
- Awake monkeys
- Awake humans
Infraslow LFPs and QPPs

Pan et al., J Vis Exp 2010
Infraslow/BOLD coherence

Pan et al., NeuroImage 2013
Isoflurane

Dexmedetomidine

Pan et al., NeuroImage 2013
Time-lagged BOLD/DC correlation

Pearson correlation at different time shifts between one LFP electrode and fMRI data at every location

Rat 4, scan 2, dexmedetomidine anesthesia, electrode in left S1FL ventral-lateral to dorsal-medial propagation, positive time shifts are BOLD after LFP

Thompson et al., NeuroImage 2014
Spatial correlation

Thompson et al., NeuroImage 2014
DC EEG-MRI Correlation

Grooms et al, Brain Connect 2017
Phase amplitude coupling

Tort et al., J Neurophysiol 2010; Thompson et al., Front Integ Neurosci 2014
Phase amplitude coupling

Thompson et al, Front Integ Neurosci 2014
Correlation vs. partial correlation

**Isoflurane**
- 0.01-0.17Hz amplitude
- fMRI

**Dexmedetomidine**
- 0.09-0.29Hz amplitude
- fMRI

- **β power** (15-25Hz)
- fMRI

- **δ/θ power** (1-9Hz)
- fMRI

**Time shift (s)**
- Standard correlation
- Partial correlation

- Significantly different partial vs. standard correlation

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Thompson et al, Front Integ Neurosci 2014
QPPs contribute to functional connectivity

4D Template

\( \ast \)

Time course of template strength

Regress from original signal
QPPs and functional connectivity

Change in BOLD variance after regression of QPPs

Significant changes in PCC connectivity after QPP regression
No change in QPP strength or timing…

…but QPP phase predicts reaction time variability.
Other tasks

Flanker

Global/local
QPP Strength

12 subjects; 3T; 22 slices; TR 700 ms; TE 30 ms; multiband factor of 2; 484 scans
QPP frequency

Two groups have means significantly different from Resting State.
QPPs in ADHD

- QPPs are linked to attention levels
- QPPs are linked to infraslow electrical activity
- QPPs are involved in task performance

Are QPPs altered in ADHD?
Where do QPPs come from?

1. Self-organization of brain activity
2. Neuromodulatory input
3. Combination of 2 and 3
Self organization?

Neural mass models (Kuramoto and Fokker Plank) combined with structural connectivity from DTI approximate empirical functional connectivity
Self organization?

QPPs are present in the models but less complex than in real data → only partially emergent from structure
Rats were given DSP-4 to selectively kill locus coeruleus neurons.

QPPs in DSP-4 rats were weakened to the point of undetectability.
QPP Summary

- Present across a variety of species and conditions
- Remarkably similar across subjects
- Linked to infraslow electrical activity
- Involved in attention and task performance
- Contribute significantly to functional connectivity
- Altered in ADHD, maybe other neurological or psychiatric disorders
- May reflect a combination of neuromodulatory input from the arousal system and the structure of the network
Dimensionality reduction

- Simulations show that analysis of raw data performs better than SWC (Shakil et al., NeuroImage 2016)
- Assume each scan is one time point in highly dimensional space
- T-distributed stochastic neighbor embedding (tSNE)
- Minimize K-L divergence between high dimensionality probability distribution and low dimensionality probability distribution using gradient descent

https://lvdmaaten.github.io/tsne/
Thanks to Gordon Berman, Emory University
Dimensionality reduction on rs-fMRI

- HCP data: 2*7 task scans + 4 rest from 446 volunteers; 8680 time points
  - Gambling, relational, emotional, social, motor, working memory, language
- 50 ICA components
- Continuous wavelet transform
- T-SNE
Why wavelets?

D6P1: 0.016 – 0.028 Hz
D4P1: 0.052 – 0.100 Hz
D5P1: 0.028 – 0.052 Hz

g = 2, highest IT

| IT | |C| |
|----|---|
| 1.1547 | 34 |
| 1.1547 | 24 |
| 1.1547 | 22 |

g = 50, lowest IT

| IT | |C| |
|----|---|
| 0.65603 | 6262 |
| 0.62921 | 6217 |
| 0.60816 | 6169 |
Similarity between mappings

Billings et al, NeuroImage 2017
Billings et al, NeuroImage 2017
tSNE trajectories

WPT_CWT_Manifold_v05.mp4
tSNE trajectories

• Can calculate probability of pairwise transition between nodes
• Subset of nodes for each condition account for majority of transitions
• Some evidence of “trajectories” of states
tSNE trajectories

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Future Directions

• More sophisticated calculations of brain trajectories
• The brain as a dynamical system
  • Attractors?
  • Metastability?
  • Perturbations?
• Better sensitivity to neural activity, less contamination from noise
• Better understanding of neurophysiology underlying BOLD signal
Acknowledgments

Funding: NIH 1 R21NS057718-01, NIH 1 R21NS072810-01, NIH 1 R01NS078095-01, NSF INSPIRE, GT FIRE, NIH BRAIN Initiative, Center for Systems Imaging

Air Force Center of Excellence on Bio-nano-enabled Inorganic/Organic Nanostructures and Improved Cognition (BIONIC)

NIH Training Grant (Matthew)

DHS Fellowship (Garth)

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