Studying brain organization via spontaneous fMRI signal

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How is the brain organized?
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- Brodmann 1905: macaque, 28 areas/hemi
- Bonin & Bailey 1947: macaque, 26 areas/hemi
- Felleman & Van Essen 1991: macaque, 80 areas/hemi
- Van Essen et al., 2011: macaque, 129 areas/hemi

Brodmann, 1905
How is the brain organized?

- Progress in humans slower
- Invasive techniques can’t be used: tracers, penetrations, etc.
- Limitations of non-invasive techniques
  - Spatial resolution: EEG, MEG
  - Temporal resolution: PET, fMRI
- Newer non-invasive techniques may accelerate progress
  - Resting state functional connectivity MRI (RSFC)
Resting state functional connectivity MRI

- Subjects lie in the scanner
- Record spontaneous T2* signal
- Brain volume every 2-3 sec (or less)
- ~3 mm cubes (or less)
- Low frequencies most powerful (< 0.08 Hz)
- Analyses are correlation-based
- High correlations imply relationships
Resting state functional connectivity MRI
Resting state functional connectivity MRI

- $r = 0.72$

- BOLD

- $r = 0.72$

- time (minutes)
Resting state functional connectivity MRI

$\text{BOLD}$

$r = 0.82$

time (minutes)
Resting state functional connectivity MRI

$r = 0.03$

BOLD

time (minutes)
Resting state functional connectivity MRI

$r = 0.07$
Resting state functional connectivity MRI

$r = 0.01$

Lateral surface

BOLD

time (minutes)

$r = 0.01$
Resting state functional connectivity MRI
Resting state functional connectivity MRI
Resting state functional connectivity MRI

Modeled activity
during finger tapping

High correlations
in spontaneous signal

Biswal et al., 1995
Resting state functional connectivity MRI

- These early studies established
  - Correlated signals present in many locations
    - Motor, visual, auditory, etc.
  - Unlikely due to artifact: cardiac, respiratory, etc.
  - Low frequencies (<0.08 Hz) contained most power
  - Spatial pattern of correlations recapitulated evoked activity

- Despite this, most neuroscientists were indifferent (at best)
  - “Rest” is uncontrolled, unspecified, unconstrained
  - fMRI signal seems likely to be dominated by noise
Resting state functional connectivity MRI

Task-induced deactivation in PET meta-analysis

High correlations in spontaneous signal

Shulman et al., 1997

Greicius et al., 2003
This 2003 finding turned heads
Followed by reports on correlations among
  attention systems: Fox, 2006
  executive control systems: Seeley, 2007; Dosenbach, 2007

These reports recapitulated spatial patterns known from PET or task fMRI. They were essentially confirmatory, building confidence in the technique.

Soon, though, fundamentally new knowledge emerged.
Resting state functional connectivity MRI

- Dorsal attention system
  - Fox et al., 2006

- Salience system
  - Seeley et al., 2007
Resting state functional connectivity MRI

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Resting state functional connectivity MRI

Fox et al., 2005
Resting state functional connectivity MRI

- Default regions deactivate during most tasks (known)
- Attention regions activate during most tasks (known)
- In the absence of tasks, ongoing signals in these two classes of brain region are anti-correlated (not known)

- RSFC began to move beyond confirmatory analyses.
Resting state functional connectivity MRI

- Does RSFC reflect experience? Individual characteristics?
- How does RSFC relate to ongoing behavior?
- What neural processes are reflected in RSFC?
- Can RSFC discriminate pathology?
- How does RSFC relate to anatomical connectivity?
- Can RSFC be used in ways analogous to tracers?
- We have gone from known systems to finding correlations between those regions. Can we go in reverse? Learn new functional systems from the patterns in RSFC?
Resting state functional connectivity MRI

- RSFC now studied in macaques, mice, rats, pigeons
- RSFC patterns are similar in light sleep, and light anesthesia
- RSFC patterns are recapitulated by ECoG and LFPs
  - high gamma frequencies in particular
- RSFC modulated by experience, scales with behavior
  - perceptual learning, motor learning, cognitive training
- RSFC patterns persist during task performance
- RSFC reflects mono- and poly-synaptic connectivity
  - e.g., cerebellar RSFC, eccentric V1 bilaterality in macaques
Resting state functional connectivity MRI

- RSFC
  - appears to be evolutionarily conserved
  - not strongly reflective of conscious thought
  - is energetically costly
  - has amplitudes similar/greater than evoked activity
  - reflects anatomy and function

- “Default mode” patterns reported in macaques, mice...
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Wig et al., 2014

Area 17 – Cytoarchitecture (Probabilistic)
Area 18 – Cytoarchitecture (Probabilistic)
RSFC Boundaries
A specific set of RSFC analyses

- Now, we will follow a specific line of results... my own
- Building network representations of the healthy adult brain
- Deriving properties of brain locations
- Making predictions about the effects of lesions
- Testing those predictions
Resting state functional connectivity MRI
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A theoretical challenge: defining networks

- Network analyses are just math
- A network is just nodes and edges (between nodes)
- Network definition **strongly** influences network properties
- If your network is well-defined
  - The math will work
  - Network properties hopefully represent the system
- If your network is badly defined
  - The math will work
  - But network properties will be inaccurate
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A theoretical challenge: defining networks

AAL atlas

Seed maps

“The most striking result [of our study] was that the use of functionally inaccurate ROIs (when defining the network nodes and extracting their associated timeseries) is extremely damaging to network estimation; hence, results derived from inappropriate ROI definition (such as via structural atlases) should be regarded with great caution.”

-Stephen Smith et al., 2011
A theoretical challenge: defining networks

Meunier et al., 2009, NI
5/90 ROIs “connector” hubs by high within-module degree and high PC

Meunier et al., 2010 Front. Neurosci.
“connector” hubs by high within-module degree and high PC
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A theoretical challenge: defining networks

264 ROIs, our best guess for area/nucleus coordinates
(from task fMRI, also from fc-Mapping)
Network modules

Pearson correlation, 52 healthy young adults
Network modules

Pearson correlation, 52 healthy young adults

Infomap algorithm

Edge density
Network modules

Pearson correlation, 52 healthy young adults

Infomap algorithm

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Infomap algorithm

Edge density

10% 2%
Network modules

weaker correlations

stronger correlations
Network modules

weaker correlations

stronger correlations
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Weaker correlations

Stronger correlations
Network modules

weaker correlations

stronger correlations
Network modules

The 10 ICA components of Smith et al., 2009

Resting state clusters of Yeo et al., 2011

Resting state clusters of Power et al., 2011

- Visual
- Default
- Cingulo-opercular
- Fronto-parietal
Network modules

Unfamiliar communities: under-recognized systems?
Network modules

Resting state clusters
- Yeo et al., 2011
- Power et al., 2011

Task fMRI activation
- Power et al., 2011
- Nelson et al., 2013

Resting state ICA components
- Zang et al., 2014
- Doucet et al., 2011

"Myelin mapping"
- Glasser et al., 2011

<table>
<thead>
<tr>
<th>Age of subjects (years)</th>
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<tbody>
<tr>
<td>7</td>
</tr>
<tr>
<td>% subjects IC detected</td>
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<tr>
<td>100</td>
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T1/T2 intensity ratio
Translating model properties into brain properties

Creating a model of the brain

A BIG GAP

Translating model properties into brain properties
Translating model properties into brain properties

Modules

Participation coefficient
Translating model properties into brain properties

Are there especially important nodes?
Translating model properties into brain properties

Degree ~ importance

Degree ~ largest modules

Strong relationship

\[ R^2 \approx 0 \]

\[ R^2 = 1 \]
Translating model properties into brain properties

State-based model

Acreage-based model

incorrect hubs in AK

hub in CA
Translating model properties into brain properties

An interpretation of RSFC degree in voxel-based models

A hierarchical system

System A

Area 1
Area 2

System B

Area 3
Area 4

Volumetric model

Area 1
Area 2
Area 3
Area 4

Degree

min
max
Translating model properties into brain properties

Studies illustrating node degree centrality (or versions of strength centrality)

- Buckner et al., J. Neurosci. 2009
- Cole et al., Neuroimage 2010
- Tomasi & Volkow, Neuroimage 2011
- Power et al., Neuron 2013
- Achard et al., PNAS 2012
Translating model properties into brain properties

Multi-system deficits

Single-system deficits
Translating model properties into brain properties
Translating model properties into brain properties

Participation coefficient
Main Conclusions

• RSFC
  • is growing in popularity
  • reflects aspects of brain organization
  • has relevance to traits, ongoing behavior, and disease

• is poorly understood
  • what processes contribute?
  • what function(s)?

• helps make simple models of a complex thing
Main Conclusions

- Some reviews on resting state:
  - Raichle, 2010. Two views of brain function. TICS.