“Resting-state” fMRI

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Overview of SPM – Resting state fMRI

- Image time-series
- Kernel
- Design matrix
- Statistical parametric map (SPM)

- Realignment
- Smoothing
- General linear model

- Normalisation
- Template

- Parameter estimates
- Statistical inference

- Gaussian field theory

$p < 0.05$
‘Exponential’ interest

Scopus search: (“functional Magnetic Resonance Imaging” OR “functional MRI” OR “fMRI”) AND (((rest OR resting) AND connectivity) OR “resting state” OR “spontaneous fluctuations” OR “intrinsic fluctuations”)

Pawela & Biswal (2011) *Brain Connectivity*

Birn (2012) *NeuroImage*
Paradigm shift

- Functionality: Local → Distributed

Kanwisher et al. (1997)
*J Neurosci*
Paradigm shift

- Functionality: Local ➡️ Distributed

Kanwisher et al. (1997)  
*J Neurosci*

Haxby et al. (2001)  
*Science*
Paradigm shift

• Functionality: Local → Distributed
• How can we characterise systems?
• How can we characterise systems-level variability?
• Translational research; Clinic ←→ Lab
Connectivity

- Anatomical connections can be inferred
  - e.g., diffusion tensor imaging (DTI)

(... also the Human Connectome Project, NIH)
Functional connectivity (FC)

• “Temporal correlations between remote neurophysiological events” - Friston (1994), HBM

• Large-scale networks
Connectivity: structural = functional?

Quigley et al. (2003) AJNR
These aren’t the blobs you’re looking for...

Shulman et al. (1997) J Cogn Neurosci; Raichle et al. (2001) PNAS
Resting-state FC

Non-motor networks?

Greicius et al. (2003) PNAS
Diseased networks?

Healthy elderly > Alzheimer’s

Greicius et al. (2004) PNAS
Diseased networks?

Healthy, young, AD predisposed > non-predisposed

Filippini et al. (2009) *PNAS*
Diseased networks

Buckner et al. (2005) J Neurosci
Diseased networks

Seeley et al. (2009) Neuron
What’s the attraction?

- “It’s not very controlled, is it?”
- No special cognitive relevance
- Translational neuroscience - biomarkers?
- Circumvent experimental/experimenter bias
- Advantages of not having to define a specific paradigm to measure ‘cognitive’ activity
- “One man’s noise is another man’s signal”
What’s in a name?

- A note on nomenclature...

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>Resting(-state)</td>
<td>Connectivity</td>
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<tr>
<td>Intrinsic</td>
<td>Activity</td>
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<tr>
<td>Endogenous</td>
<td>Oscillations</td>
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<tr>
<td>Spontaneous</td>
<td>Fluctuations</td>
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<tr>
<td>Task-free/-independent</td>
<td>Witchcraft etc. ...</td>
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</tbody>
</table>

- “Resting-state” as a product of the method, not the interpretation
Resting-state networks (RSNs)

- Multiple spatial patterns of temporally correlated activity

Beckmann et al. (2005) *Phil Trans R Soc Lond B*
Resting-state networks (RSNs)

- Multiple spatial patterns of temporally correlated activity
- RSNs reflect distinct, large-scale neuronal functional systems
- Can be identified in absence of strictly-defined models

Smith et al. (2009) PNAS
Resting-state networks (RSNs)

- Spatial characteristics: (dys)function?

Beckmann et al. (2005) *Phil Trans R Soc Lond B*
Resting-state networks (RSNs)

- Spatial characteristics: (dys)function?

Smith et al. (2009) PNAS
RSN connectivity: structural = functional

Greicius et al. (2008) Cereb Cortex
Grey Matter Density Confound

Correlation with white matter structure

Voets et al. (2012) Brain
Resting-state FC analysis options
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1. Seed-based correlation analysis (SCA)
Resting-state FC analysis options

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2. Independent component analysis (ICA)
Resting-state FC analysis options

1. Seed-based correlation analysis (SCA)
2. Independent component analysis (ICA)
3. Psycho-/physiological interaction (PPI) analysis?
SCA in SPM
Analysis pros & cons: SCA

Cole et al. (2010)
Front Syst Neurosci

1. Seed-based correlation analysis: ‘mass univariate’ approach
Analysis pros & cons: SCA

2. Independent component analysis: ‘multivariate’ approach

Cole et al. (2010) Front Syst Neurosci
Analysis pros & cons: SCA

• Direct answer to a direct question...
  – What ‘network’ of regions is most strongly correlated with the BOLD signal of my ROI?

• Can the results of seed-based FC analyses be fully described as forming a ‘network’, neurobiologically speaking?
  – As many networks as possible seeds (each voxel)

• Connectivity ‘nonstationarity’

• Global signal regression
Between-network interactions

• RSN temporal characteristics (e.g., ‘nonstationarity’)?
Between-network psychopathology model

Menon (2011) TICS
The dilemma of global signal regression

• **PRO:** aids with removal of non-neuronal noise from seed-based analyses

• **CON:** artificially enhances and/or induces negative (/anti-)correlations

Murphy et al. (2009) *NeuroImage*
Independent component analysis (ICA)

Beckmann et al. (2005) Phil Trans R Soc Lond B
Independent component analysis (ICA)

• Finds projections (components) of maximal independence in non-Gaussian data using higher-order (multivariate) statistics

• Multiple software packages for applying ICA to fMRI
  - FSL MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components)
  - GIFT
  - ICASSO... etc.
ICA-based parcellation

In preparation...
Analysis pros & cons: ICA

- ICA does not require *a priori* knowledge of time courses or spatial maps / regions of interest

- Resulting components can be thought of as ‘networks’, perhaps more representatively than the results of seed-based analyses

- ICA also provides a valuable de-noising tool; signal components suffer less artefact intrusion
  - other ICs account for structured noise effects
  - Single-session ICA-based cleanup - e.g., Salimi-Khorshidi et al. (2014) *NeuroImage*
Analysis pros & cons +

- Noise components
- Slice ‘drop-outs’

Thanks to C. Beckmann for examples.
Analysis pros & cons +

- Noise components
- Gradient instability

Thanks to C. Beckmann for examples
Analysis pros & cons +

- Noise components
- EPI ‘ghost’ artefacts

Thanks to C. Beckmann for examples
Analysis pros & cons +

- Noise components
- High-frequency (pulsatile?) noise

Thanks to C. Beckmann for examples
Analysis pros & cons +
Analysis pros & cons +

- Noise components
- Head motion

Thanks to C. Beckmann for examples
Motion aside...

- Huge debate about the importance of strictly controlling for motion/micro-motion confounds in FC analyses

Power et al. (2012)
*NeuroImage*
Analysis pros & cons: ICA

• ICA: Model order selection - what is the ‘correct’ number of components for a given data set?

• ‘Splitting’ / ‘fusing’ of components: levels of neurobiological complexity, or mathematical ‘crowbarring’?

• How does one decide which components are ‘of interest’/functional relevance/neuronal in origin?

• Nonstationarity again...Temporal ICA? - Smith et al (2012) PNAS
Multi-session RSN identification: concat-ICA

Multi-session RSN comparison: dual regression

1. \[ \text{FMRI data S1} \times \text{group ICA maps} = \text{voxels} \times \text{#components} \times \text{time courses S1} \]

2. \[ \text{FMRI data S1} \times \text{time courses S1} = \text{spatial maps S1} \]

3. Repeat \( \times N \); then random-effects test

Alternative methods

• Graph theoretical approaches
  - ‘Nodes’ & ‘Edges’
  - What’s your cut-off point?

• Amplitude of low-frequency fluctuations (ALFF)

• Regional homogeneity (ReHo)

• Clustering
Alternative methods

• Seed-based *partial* correlation analysis
  - ‘Parcellation’ of functional regions based on seed-to-target functional connectivity strengths
  - Topographic connectivity

O’Reilly et al. (2010) *Cereb Cortex*
To do...

- Validate resting-state fMRI characteristics in terms of their qualities as biomarkers
- Fully explore the classification accuracy of resting-state relative to, e.g., task-fMRI
- Continue recent trend in data-sharing & meta-analytic approaches
- Imbue cognitive relevance by moving the emphasis from ‘resting’ to ‘mental’ state networks
To do...

- Validate resting-state fMRI characteristics in terms of their qualities as biomarkers
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Detecting subgroups of patients in schizophrenia

- three distinct subgroups (total N=41)
- subgroups differ (p < 0.05) wrt. negative symptoms on the positive and negative symptom scale (PANSS)

Brodersen et al. (2014) Neuroimage: Clinical
Classifying populations & individuals

• Age & Sex-related variability - Biswal et al. (2010) PNAS
Classifying populations & individuals

• Age & Sex-related variability - Biswal et al. (2010) PNAS

• However; ‘ADHD-200’ competition: personal characteristic data (site of data collection, age, gender, handedness, IQ) outperformed fMRI data under a logistic classifier*

*Brown et al. (2012) Front Syst Neurosci
Resting-state ‘effective connectivity’?

- “The influence one neural system exerts over another” - Friston (1994), *HBM*
- Lag-based methods; Granger Causality
- (Stochastic/spectral) DCM
- High temporal-resolution acquisitions
- ‘Multiband’ acquisitions
Resting-state ‘effective connectivity’?

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‘Mechanistic’ analysis of resting-state fMRI data

Kahan et al
(2014) Brain
‘Mechanistic’ analysis of resting-state fMRI data

Kahan et al (2014) Brain
‘Mechanistic’ analysis of resting-state fMRI data

• More advanced/abstract cognitive models?
• Other neuromodulatory systems?
• Hypothesis-driven
• Informed by key historical work across multiple levels of biological complexity
• Maximise utility for future applications in neuropsychiatry & drug development
Further reading


- Smith et al. (2013) Functional connectomics from resting-state fMRI. *Trends Cogn Sci* 17:666-682