Introduction to functional connectivity MRI

Koene Van Dijk, PhD
Why
Spontaneous Activity Within Seed Region

Biswal et al., MRM, 1995
SEED BASED  
ICA

MOTOR
z=57
R

VISUAL
z=0

DEFAULT
z=26

ATTENTION
z=54

Van Dijk et al., 2010

Yeo et al., 2011
Functional connectivity MRI (fcMRI)

Measures temporal coherence among brain regions (Biswal et al., 1995)

Shows existing functional-anatomical networks

Most networks show coherent activity both during rest and during tasks (Fransson, 2006; Krienen et al., 2014)
• **Methods:**
  – Seed based analysis
    • Removal of physiological noise
  – Independent component analysis (ICA)
  – Confounding effects of head motion

• **Future directions**
  – Higher field strength offers higher spatial resolution
  – Simultaneous Multi-Slice (SMS) acquisition offers higher temporal resolution
Seed based analysis

• Standard fMRI pre-processing:
  – Slice timing correction
  – Motion correction
  – Spatial normalization to common atlas space (Talairach / MNI)
  – Spatial smoothing (Gaussian filter)

• Additional pre-processing:
  – Bandpass filter (retaining frequencies slower than ~0.08 Hz)
  – Removal of any residual effects of motion by regressing out the motion correction parameters
  – Removal of physiological noise
Removal of physiological noise

Low frequency BOLD fluctuations

Carbon dioxide fluctuations

Biswal et al., 1995
Wise et al., 2004
Removal of physiological noise

- **By regressing out** signals in the brain that are believed to contain noise:
  
  - Signal from ventricles
  - Signal from white matter
  
  - Signal averaged over the whole brain (Desjardins et al., 2001; Corfield et al., 2001; Macey et al. 2004)

(Dagli et al. 1999; Windischberger et al. 2002)
Ventricles and white matter signal
Whole brain signal is related to end-tidal carbon dioxide during periods of hypercapnia.
Whole brain signal

Pros:

• Captures breathing variations (Corfield et al., 2001)

• Known to remove noise (Macy et al., 2004)

• Increased specificity of functional connectivity maps of the motor system (Weisenbacher et al., 2009)

• Shows fine neuroanatomical specificity not seen without global signal correction (Fox et al., 2009)

See for discussion: Vincent et al., 2006; Fox et al. 2009; Murphy et al. 2009; Weissenbacher et al., 2009; Van Dijk et al., 2010; Saad et al., 2012
Whole brain signal

Cons:

See for discussion: Vincent et al., 2006; Fox et al. 2009; Murphy et al. 2009; Weissenbacher et al., 2009; Van Dijk et al., 2010; Saad et al., 2012
Whole brain signal

What does this practically mean?

• Whenever possible collect heart rate (with e.g. pulse oximeter or ECG) and respiration signals (with e.g. a pneumatic belt around the abdomen or with a mouth piece that measures airflow)

• Removal of the whole brain signal is a viable step especially if one has not measured the actual variability in heart rate and respiration

• Negative correlations after whole-brain signal regression should be interpreted with utmost caution

• Do consider alternative noise removal strategies (e.g. Compcor, FIX)

See for discussion: Vincent et al., 2006; Fox et al. 2009; Murphy et al. 2009; Weissenbacher et al., 2009; Van Dijk et al., 2010; Saad et al., 2012
Removal of physiological noise

• By regressing out signals in the brain that are believed to contain noise:
  
  – Signal from ventricles
  
  – Signal from white matter (Dagli et al. 1999; Windischberger et al. 2002)
  
  – Signal averaged over the whole brain (Desjardins et al., 2001; Corfield et al., 2001; Macey et al. 2004)

• By measuring variability in heart rate and respiration and regressing it out:
  
  – RETROICOR (Glover et al., 2002)
  
  – RVT (Birn et al., 2006)
  
  – RVHRCOR (Chang and Glover, 2009)

• By estimating variability in heart rate and respiration and regressing it out:
  
  – PESTICA (Beall and Lowe, 2007; 2010)
  
  – CompCor (Behzadi et al., 2007; also implemented in Sue Whitfield-Gabrieli’s Conn toolbox)
  
  – CORSICA (Perlberg et al., 2007)
  
  – FIX (Salimi-Khorshidi et al., 2014)
Basic measures of seed based analysis

A. Correlation values between regions of interest:

\[ M \text{(SD)} \]

.52 (.20)*

.64 (.31)*

B. A map from a single seed region of interest:
• **Methods:**
  
  – Seed based analysis
    
    • Removal of physiological noise
  
  – Independent component analysis (ICA)
    
  – Confounding effects of head motion

• **Future directions**
  
  – Higher field strength offers higher spatial resolution
  
  – Simultaneous Multi-Slice (SMS) acquisition offers higher temporal resolution
Independent component analysis (ICA)

Data is decomposed into a set of **spatially independent** maps and corresponding time courses

**MELODIC**: http://fsl.fmrib.ox.ac.uk/fsl/melodic/ Beckmann et al., 2005

**GIFT**: http://mialab.mrn.org/software/ Calhoun et al., 2001
Independent component analysis (ICA)

**SINGLE SUBJECT**

- **FMRI data**
- **spatial maps**

**MULTI SUBJECT**

- **FMRI data 1**
- **FMRI data 2**
- **spatial maps**

**MELODIC**: [http://fsl.fmrib.ox.ac.uk/fsl/melodic/](http://fsl.fmrib.ox.ac.uk/fsl/melodic/)  
Beckmann et al., 2005

**GIFT**: [http://mialab.mrn.org/software/](http://mialab.mrn.org/software/)  
Calhoun et al., 2001
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<tr>
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<th>Coordinates</th>
<th>Percentage</th>
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<td>(-27,-3,57)</td>
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<td>IC03</td>
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<tr>
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<td>IC05</td>
<td>(6,24,60)</td>
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<td>Percentage</td>
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Noise components

slice drop-outs

gradient instability

EPI ghost

head motion

high-frequency noise

eye-related artefacts

Beckmann et al., 2000 & http://www.fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf
Neuronal network components

Damoiseaux et al., 2006
Seed based

Pros:

• Quantification of network strength: one number per subject (easy to relate to other measures such as behavior, white matter (Andrews-Hanna et al., 2007), amyloid pathology (Hedden et al., 2009))

• Input for other other metrics: graph analytic approaches, clustering, multivariate approaches

Cons:

• One needs to choose networks based on prior knowledge of brain systems (e.g. from anatomy, seed regions from the literature)

• Methods for removal of physiological noise not without controversy (Fox et al. 2009; Murphy et al. 2009; Saad et al., 2012)

ICA

Pros:

• No prior knowledge of brain systems necessary

• Automatic removal of physiological noise (to a certain extent)

Cons:

• Obtaining one number per subject is not straightforward
Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization

Koene R. A. Van Dijk, Trey Hedden, Archana Venkataraman, Karleyton C. Evans, Sara W. Lazar, and Randy L. Buckner

- Test-retest reliability
- Effects of scan length
- Seed-based analysis versus ICA
- Differences between:
  - Two scans of 6 min versus one scan of 2 min
  - Temporal resolution: TR=2.5 versus TR=5.0
  - Spatial resolution: 2x2x2 versus 3x3x3
- Effects of task/instruction (eyes open, eyes closed, word classification task)

Free online access: http://jn.physiology.org/content/103/1/297.full
• **Methods:**
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• **Future directions**
  - Higher field strength offers higher spatial resolution
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The influence of head motion on intrinsic functional connectivity MRI
Koene R.A., Van Dijk a,b, Mert R. Sabuncu b,c, Randy L. Buckner a,b,d,e,*

Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion
Jonathan D. Power a,* , Kelly A. Barnes a, Abraham Z. Snyder a,b, Bradley L. Schlaggar a,b,c,d, Steven E. Petersen a,b,d,e

Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth
Theodore D. Satterthwaite a,* , Daniel H. Wolf a, James Loughead a, Kosha Ruparel a, Mark A. Elliott b, Hakon Hakonarson c, Ruben C. Gur a,b,d, Raquel E. Gur a,d
Decile 5 > Decile 6

Mean Motion (mm)

Frequency (%)

Female
Male

Van Dijk et al., NeuroImage 2012

Decile 5
Decile 6
Motion decreases correlation strength in large-scale networks

\[ r = -0.18 \]

\[ r = -0.16 \]

(Van Dijk et al., NeuroImage 2012)
Motion increases local functional coupling

(Van Dijk et al., NeuroImage 2012)
Interim conclusions

1. Even in compliant healthy young adults, head motion has a significant effect on measures of network strength.

2. Head motion may have different effects on functional connectivity depending on the network studied.

3. Most variance in fcMRI metrics is not related to motion.

4. Carefully consider effects of head motion in studies that contrast groups:
   - Children vs adults
   - Old vs young
   - Patients vs controls

(Van Dijk et al., NeuroImage 2012)
Causes of head motion during MRI

- Shifts in head position during the scan
- Swallowing
- Jaw clenching
- Cardiac cycles
- Respiration

Within-subject data preprocessing is not sufficient:
- Rigid body motion correction
- Regression of motion correction parameters
- Regression of signal from ventricles, white matter, and whole brain
How to minimize confounding effects of head motion

1. Prevent head motion as much as possible during the scan
Prevent head motion as much as possible during the scan

- Making sure that the subject is lying comfortable on the scanner bed.

- Making sure that there is soft padding in place: It is much easier to stay still if your head is somewhat fixated.

- Potentially use a strip of surgical paper tape placed loosely across the forehead attached to the coil on two sides.

- Taking an extra minute to have the subject think by themselves if they are as comfortable as possible and make any adjustment to pillows, blankets, mirror, pads, etc.
How to minimize confounding effects of head motion

1. Prevent head motion as much as possible during the scan

2. Removing epochs were motion occurred: “scrubbing” (Power et al., 2012)
Removing epochs were motion occurred: “scrubbing”
How to minimize confounding effects of head motion

1. Prevent head motion as much as possible during the scan

2. Removing epochs were motion occurred: “scrubbing” (Power et al., 2012)

3. Use ICA-based strategies:
   
a. FMRIB's ICA-based X-noiseifier: **FIX** (Salimi-Khorshidi et al., 2014)
   
b. Automatic Removal of Motion Artifacts: **AROMA** (Pruim et al., 2015)
ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data

Raimon H.R. Pruim\textsuperscript{a,b,*}, Maarten Mennes\textsuperscript{a,b}, Daan van Rooij\textsuperscript{b,c}, Alberto Llera\textsuperscript{b}, Jan K. Buitelaar\textsuperscript{a,b,d}, Christian F. Beckmann\textsuperscript{a,b,e}

\textsuperscript{a} Radboudumc, Donders Institute for Brain, Cognition and Behaviour, Department of Cognitive Neuroscience, Nijmegen, The Netherlands
\textsuperscript{b} Radboud University, Donders Institute for Brain, Cognition and Behavior, Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands
\textsuperscript{c} University of Groningen, University Medical Center Groningen, Department of Psychiatry, Groningen, The Netherlands
\textsuperscript{d} Karakter Child and Adolescent Psychiatry University Center, Nijmegen, The Netherlands
\textsuperscript{e} Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, Oxford, United Kingdom
**Participant level**

- **fMRI Preprocessing**
  - Motion correction
  - 4D mean intensity normalization
  - Spatial smoothing (6mm FWHM)

- **ICA-AROMA**
  - **ICA**
    - Register IC spatial maps to MNI152 2mm

- **Motion Component Classification**
  - Based on four features:
    - maximum RP correlation
    - Edge fraction
    - CSF fraction
    - High-frequency content

- **fMRI data denoising**
  - Removal of classified ICs from the fMRI data (fsl_regfilt)

- **fMRI Preprocessing**
  - Nuisance regression:
    - WM, CSF & linear trend
    - Highpass filtering

- **Statistical analysis**

(Pruim et al., NeuroImage 2015)
<table>
<thead>
<tr>
<th>*IC-label</th>
<th>Initial ICA results</th>
<th></th>
<th>After ICA-AROMA</th>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD number ICs</td>
<td>Correlation with RMS-FD (p-value)</td>
<td>Mean ± SD number ICs</td>
</tr>
<tr>
<td>Motion</td>
<td>12.4 ± 5.7</td>
<td>0.87 (&lt;1e-9)</td>
<td>0.9 ± 0.8</td>
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<tr>
<td>RSN</td>
<td>8.0 ± 2.7</td>
<td>−0.06 (0.76)</td>
<td>7.7 ± 2.8</td>
</tr>
<tr>
<td>Other</td>
<td>14.2 ± 4.7</td>
<td>0.43 (0.02)</td>
<td>2.8 ± 2.1</td>
</tr>
<tr>
<td>Total</td>
<td>34.5 ± 8.2</td>
<td>0.83 (&lt;1e-7)</td>
<td>11.4 ± 3.2</td>
</tr>
</tbody>
</table>

(Pruim et al., NeuroImage 2015)
4. Prospectively correct for motion during data acquisition \( (\text{Thesen et al., 2000; Ward et al., 2000, Tisdall et al., 2013}) \)

5. Real time feedback to indicate when movement exceeded a specified threshold \( (\text{Yang et al., 2005}) \)

6. Regress motion estimates from between-subject analyses

7. Match the level of motion between subject groups
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• Future directions
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Future directions

• Higher field strength offers higher spatial resolution
Simultaneous Multi-Slice (SMS) acquisition offers higher temporal resolution

<table>
<thead>
<tr>
<th></th>
<th>TR</th>
<th>#volumes in 6 min</th>
<th>spatial resolution</th>
<th>SMS</th>
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<tr>
<td>Standard scan</td>
<td>3000 ms</td>
<td>120</td>
<td>3 mm</td>
<td>-</td>
</tr>
<tr>
<td>SMS scan</td>
<td>350 ms</td>
<td>~1000</td>
<td>2.5 mm</td>
<td>12</td>
</tr>
</tbody>
</table>
Simultaneous Multi-Slice (SMS) acquisition offers higher temporal resolution.

Kawin Setsompop, Jonathan Polimeni
References and recommended reading

- **Van Dijk KRA et al.** (2010) Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization. Journal of Neurophysiology. 103: 297-321 [http://jn.physiology.org/content/103/1/297.full](http://jn.physiology.org/content/103/1/297.full)


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