Introduction to functional connectivity MRI

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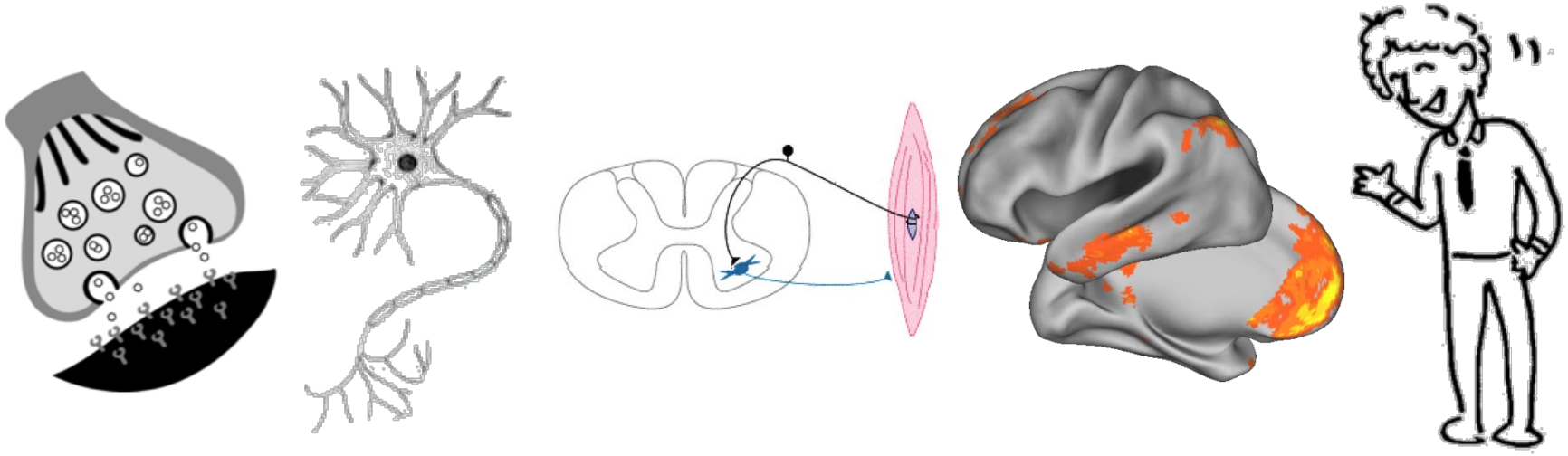
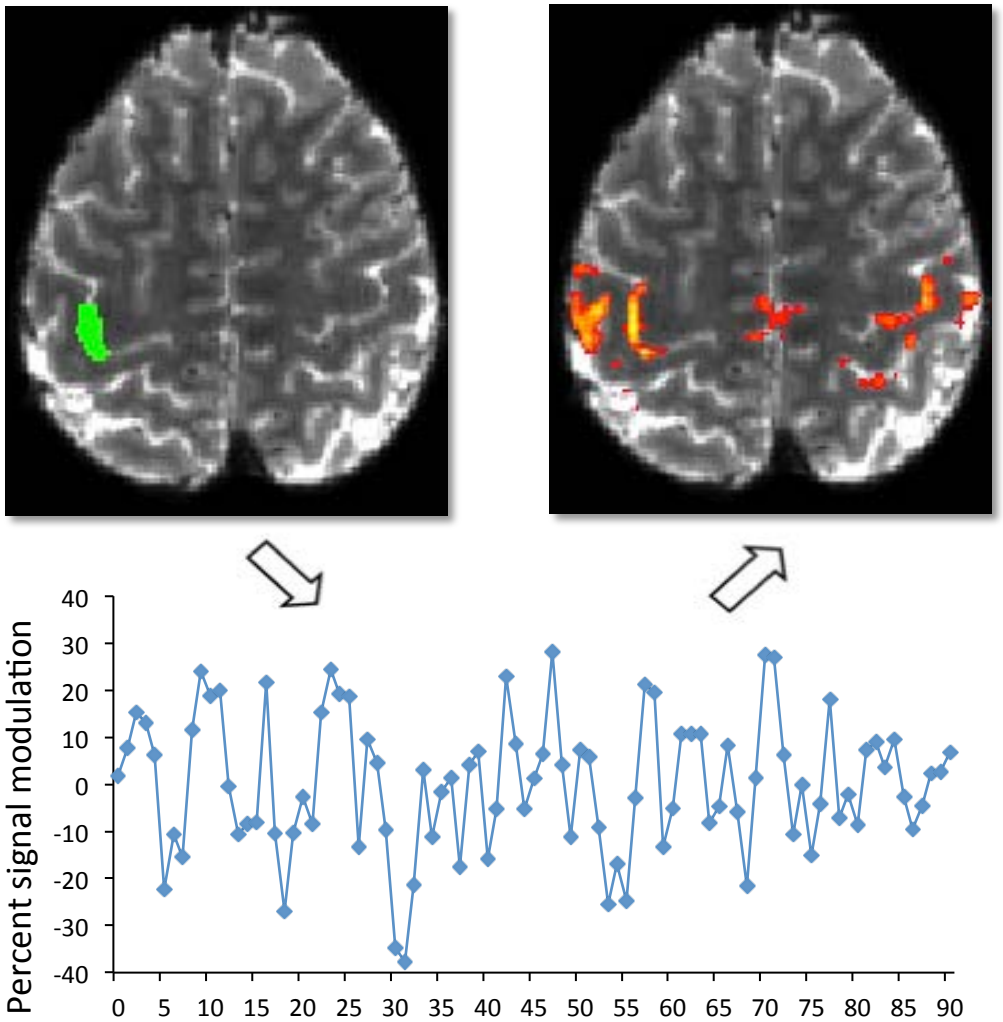
Why

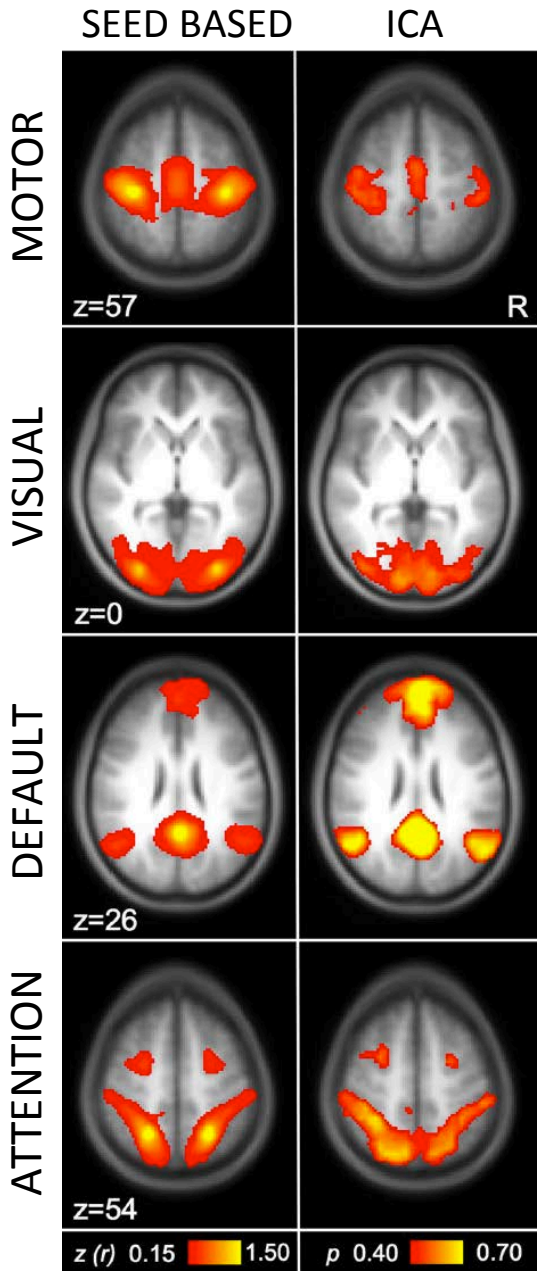


How

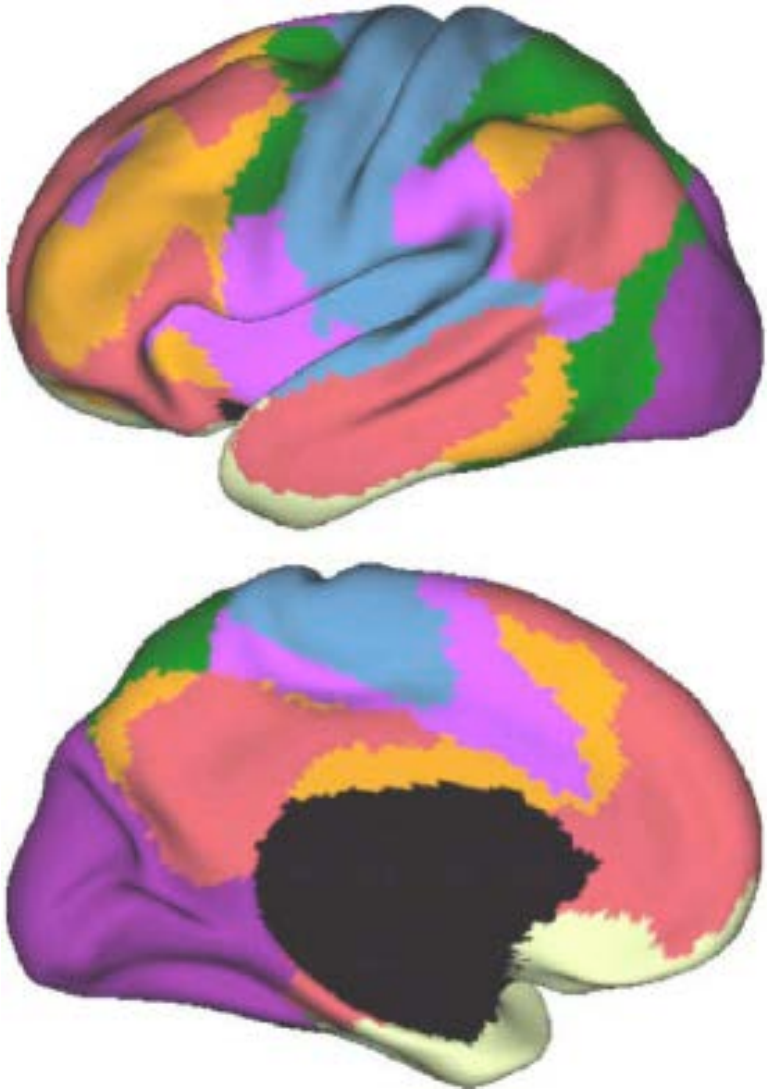


Spontaneous Activity Within Seed Region

Biswal et al., MRM, 1995



Van Dijk et al., 2010



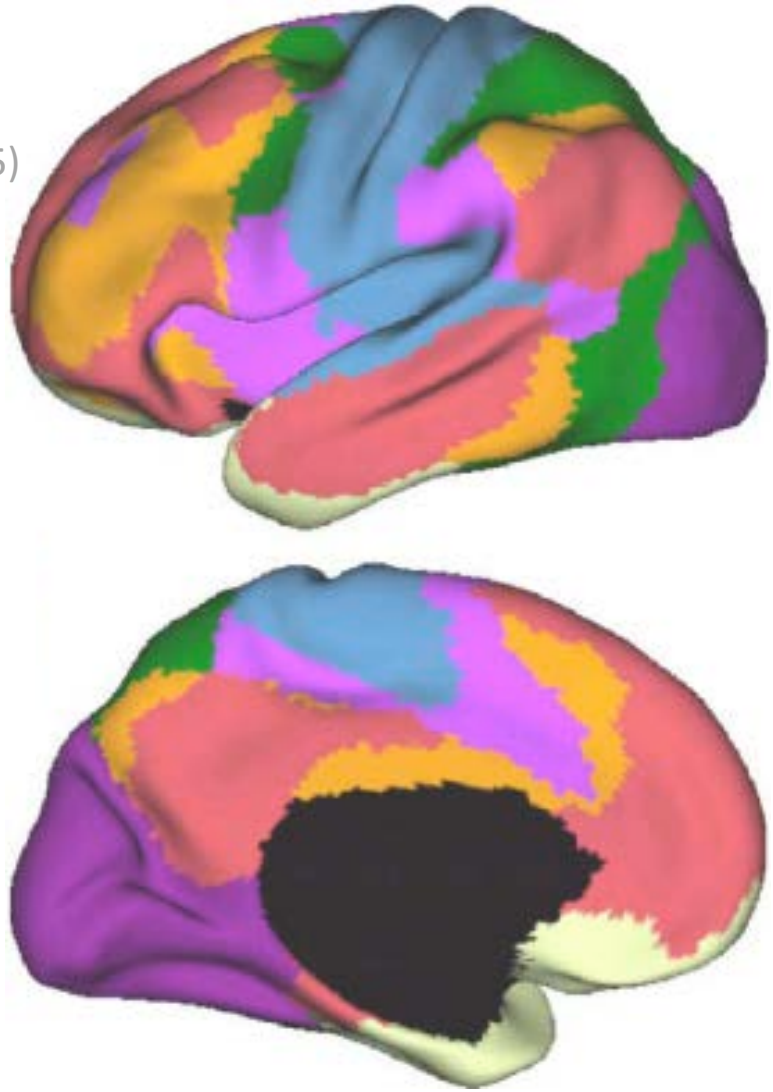
Yeo et al., 2011

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)



Yeo et al., 2011

- 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

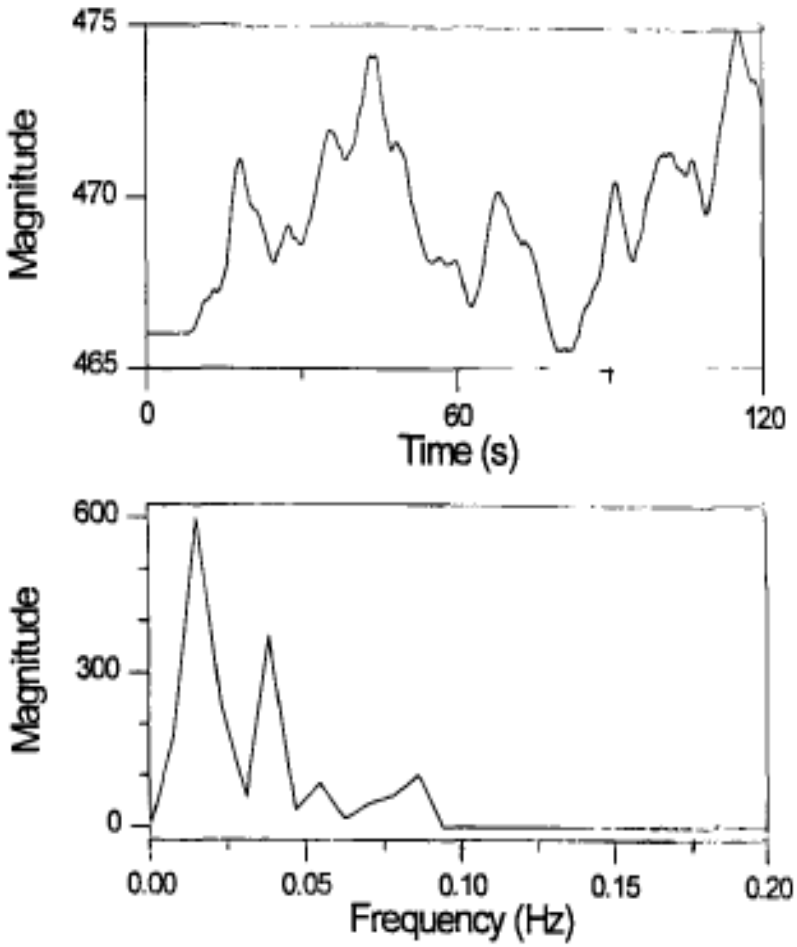
Seed based analysis

- 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

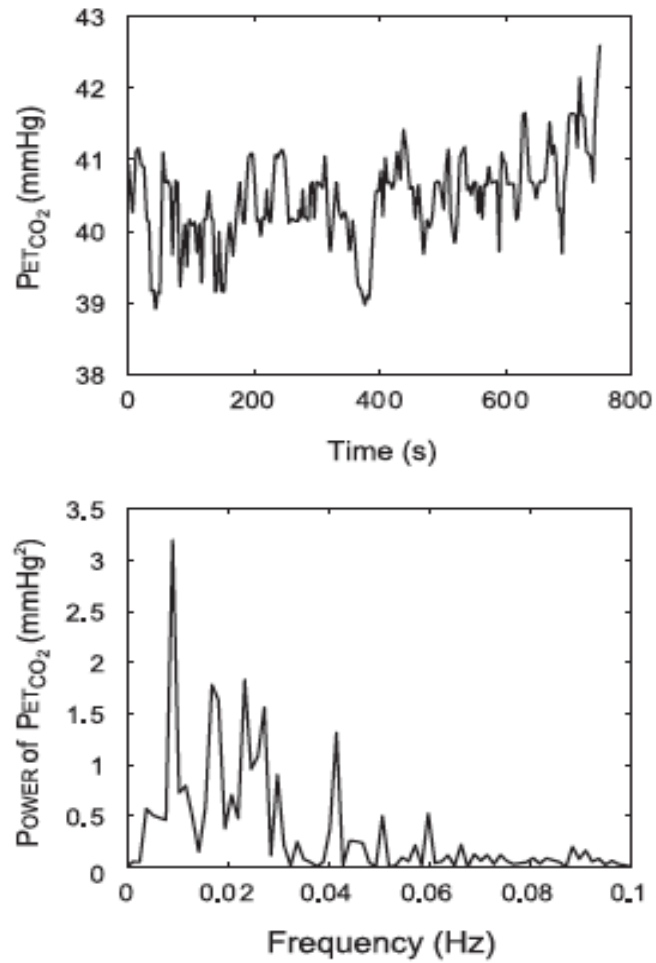
Removal of physiological noise

Low frequency BOLD fluctuations



Biswal et al., 1995

Carbon dioxide fluctuations



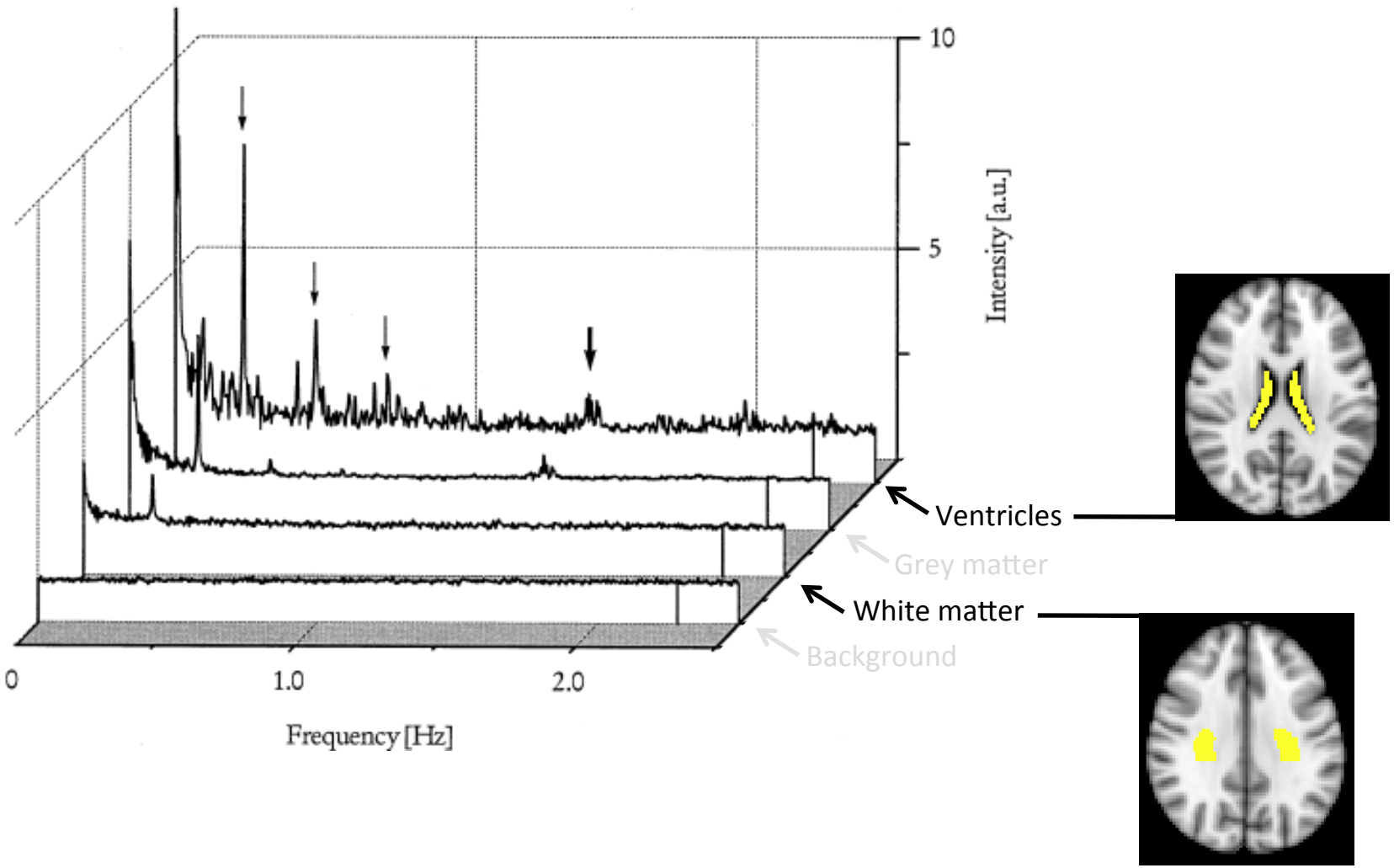
Wise et al., 2004

Removal of physiological noise

- <u>By regressing out</u> 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)

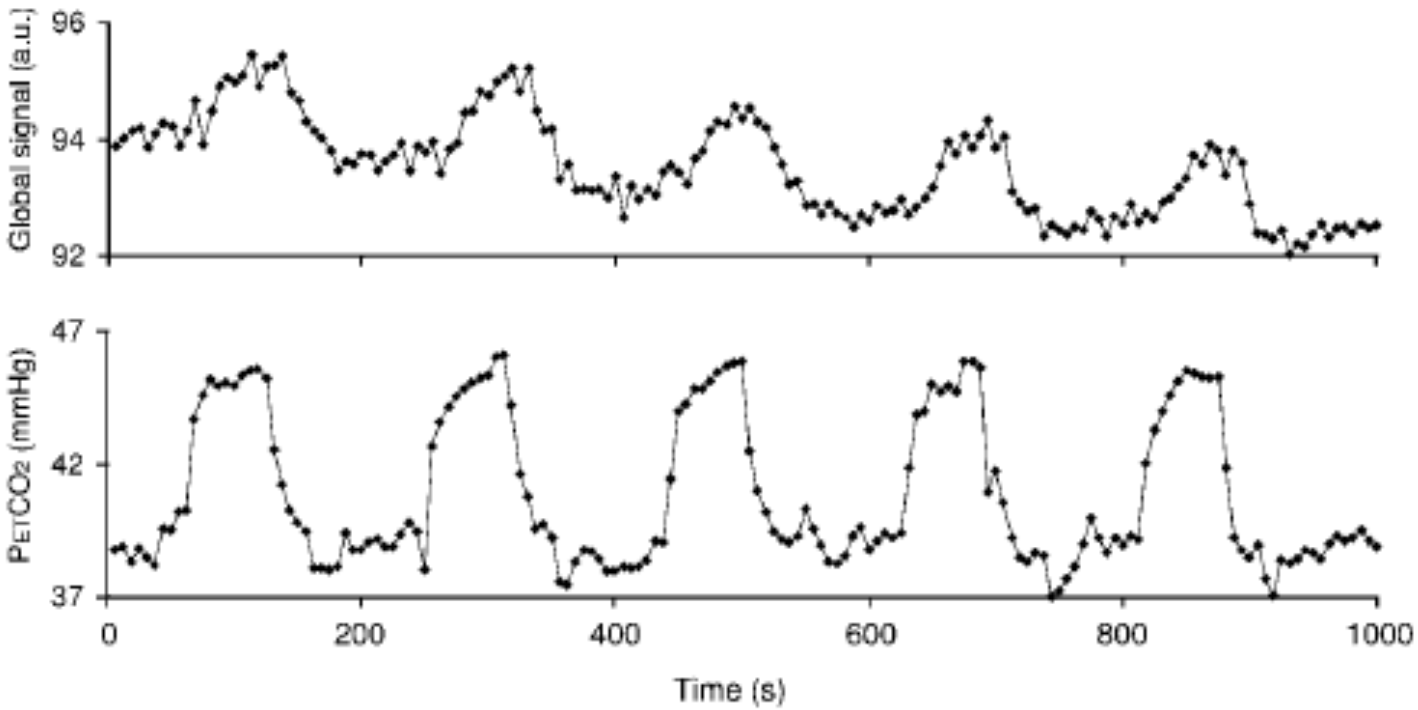
Ventricles and white matter signal

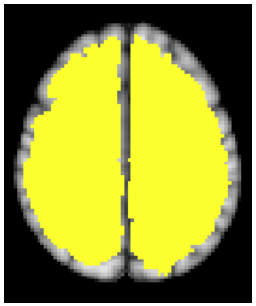


Windischberger et al. 2002

Whole brain signal

Whole brain signal is related to end-tidal carbondioxide during periods of hypercapnia

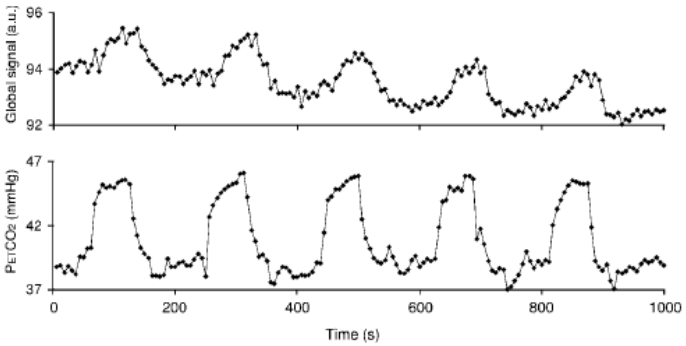




Corfield et al., 2001

Whole brain signal

Pros:

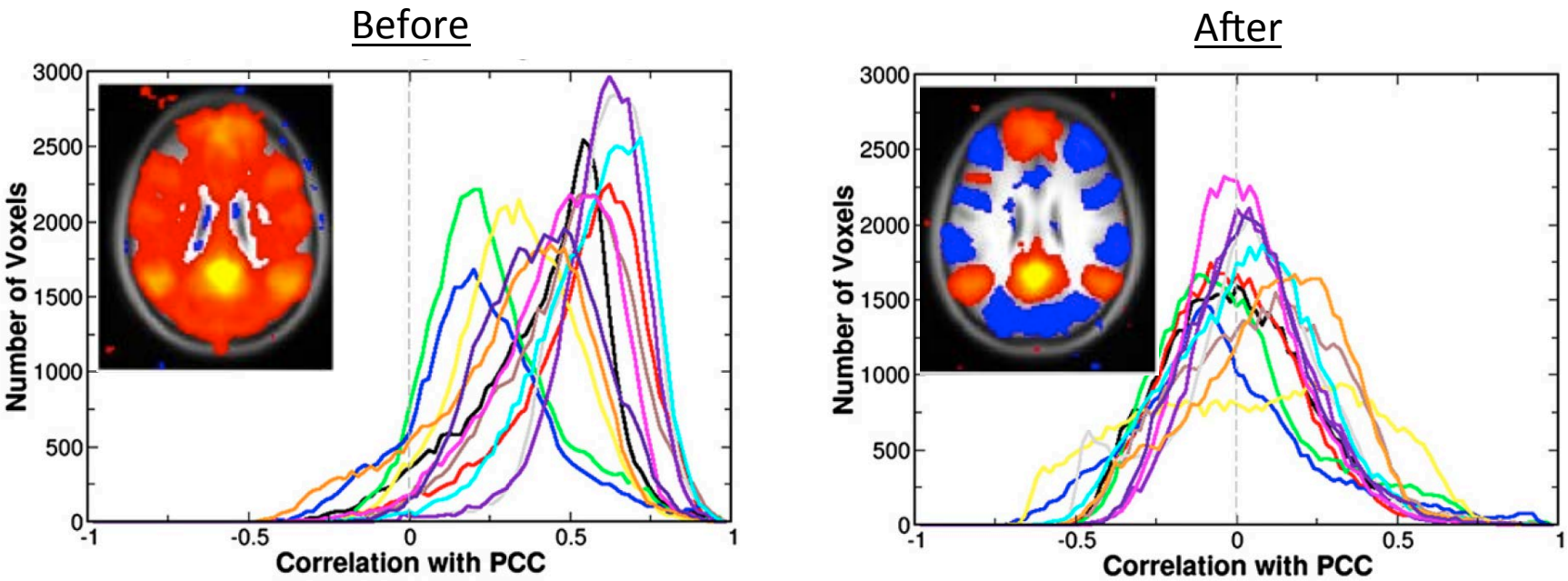


- Captures breathing variations (Corfield et al., 2001)
- Known to remove noise (Macy et al., 2004)
- Increased specificity of functional connectivity maps of the motor system (Weisenbacher et al., 2009)
- Shows fine neuroanatomical specificity not seen without global signal correction (Fox et al., 2009)

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

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    (Dagli et al. 1999; Windischberger et al. 2002)
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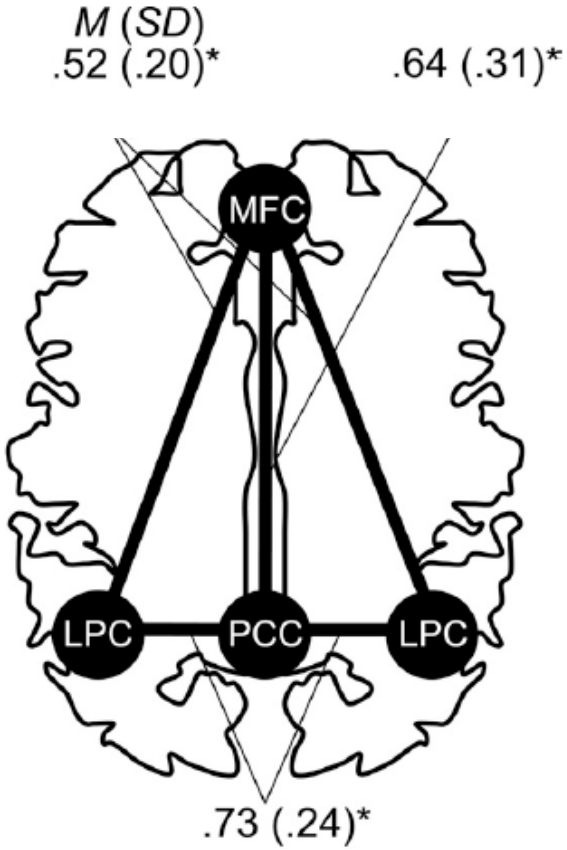
- <u>By measuring</u> variability in heart rate and respiration and regressing it out:
  - RETROICOR (Glover et al., 2002)
  - RVT (Birn et al., 2006)
  - RVHRCOR (Chang and Glover, 2009)

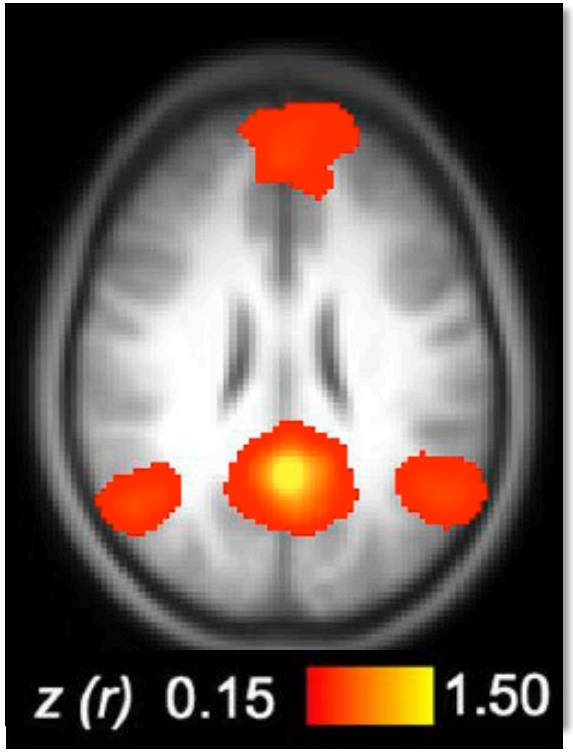
- <u>By estimating</u> variability in heart rate and respiration and regressing it out:
  - PESTICA (Beall and Lowe, 2007; 2010)
  - CompCor (Behzadi et al., 2007; **also implemented in Sue Whitfield-Gabrieli's Conn toolbox**)
  - CORSICA (Perlbarg et al., 2007)
  - FIX (Salimi-Khorshidi et al., 2014)

Basic measures of seed based analysis

A. Correlation values between regions of interest:



B. A map from a single seed region of interest:



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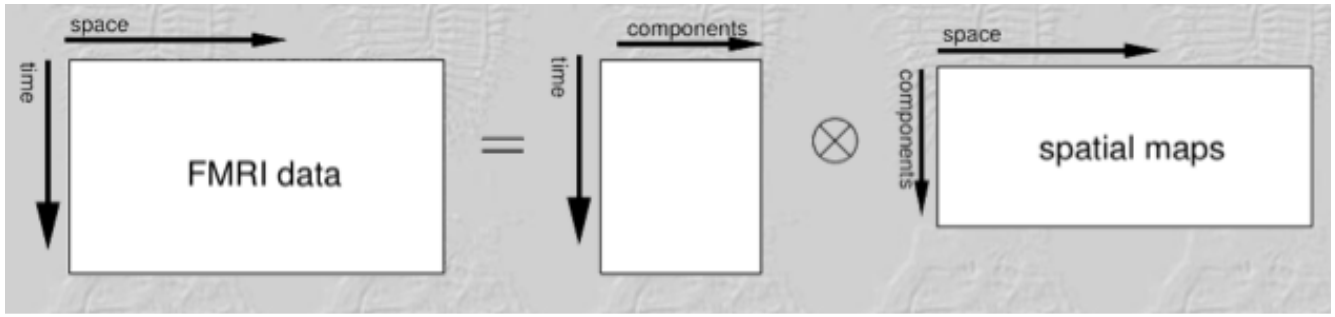
Independent component analysis (ICA)

SINGLE SUBJECT



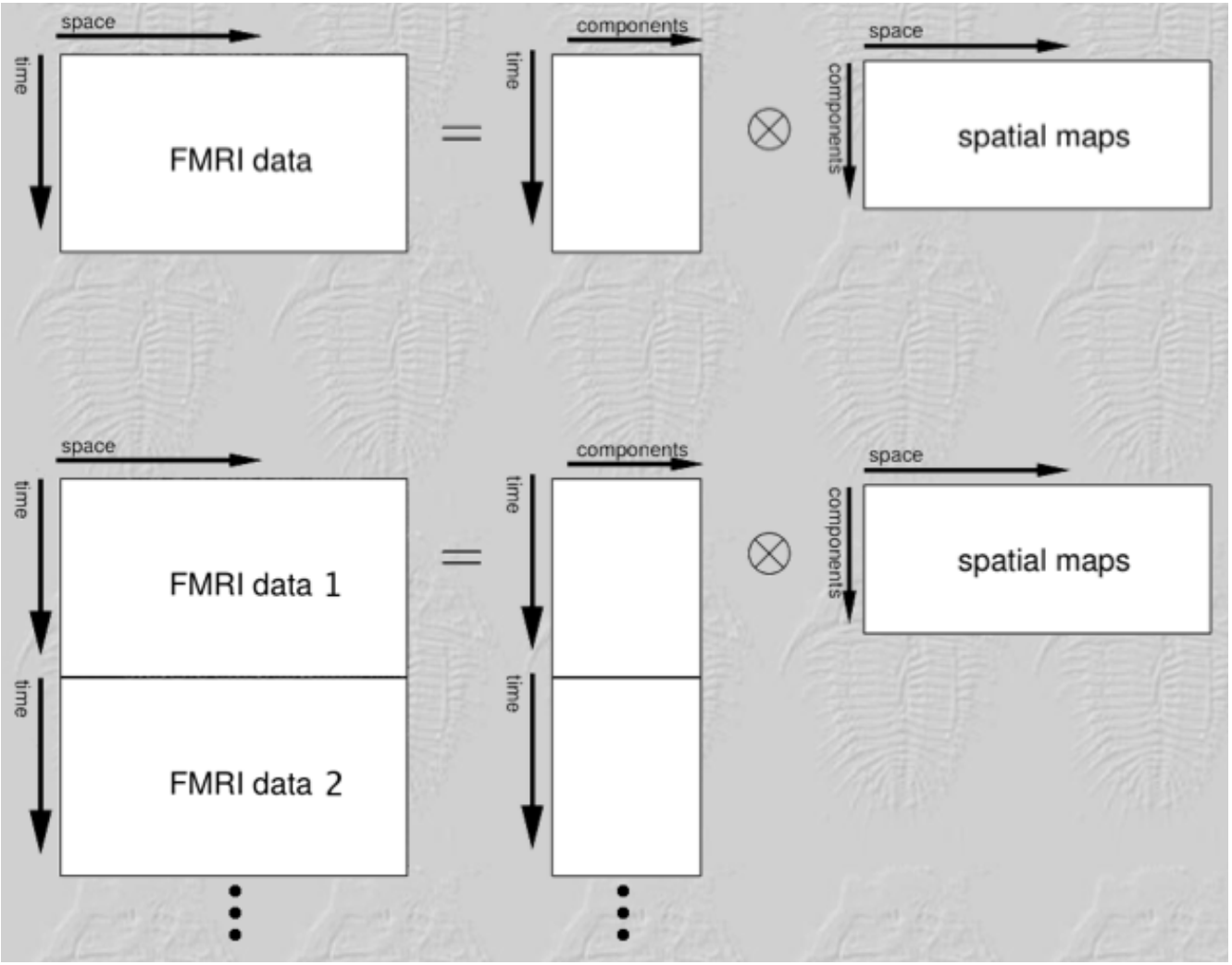
Data is decomposed into a set of <u>spatially independent</u> maps and corresponding time courses

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)

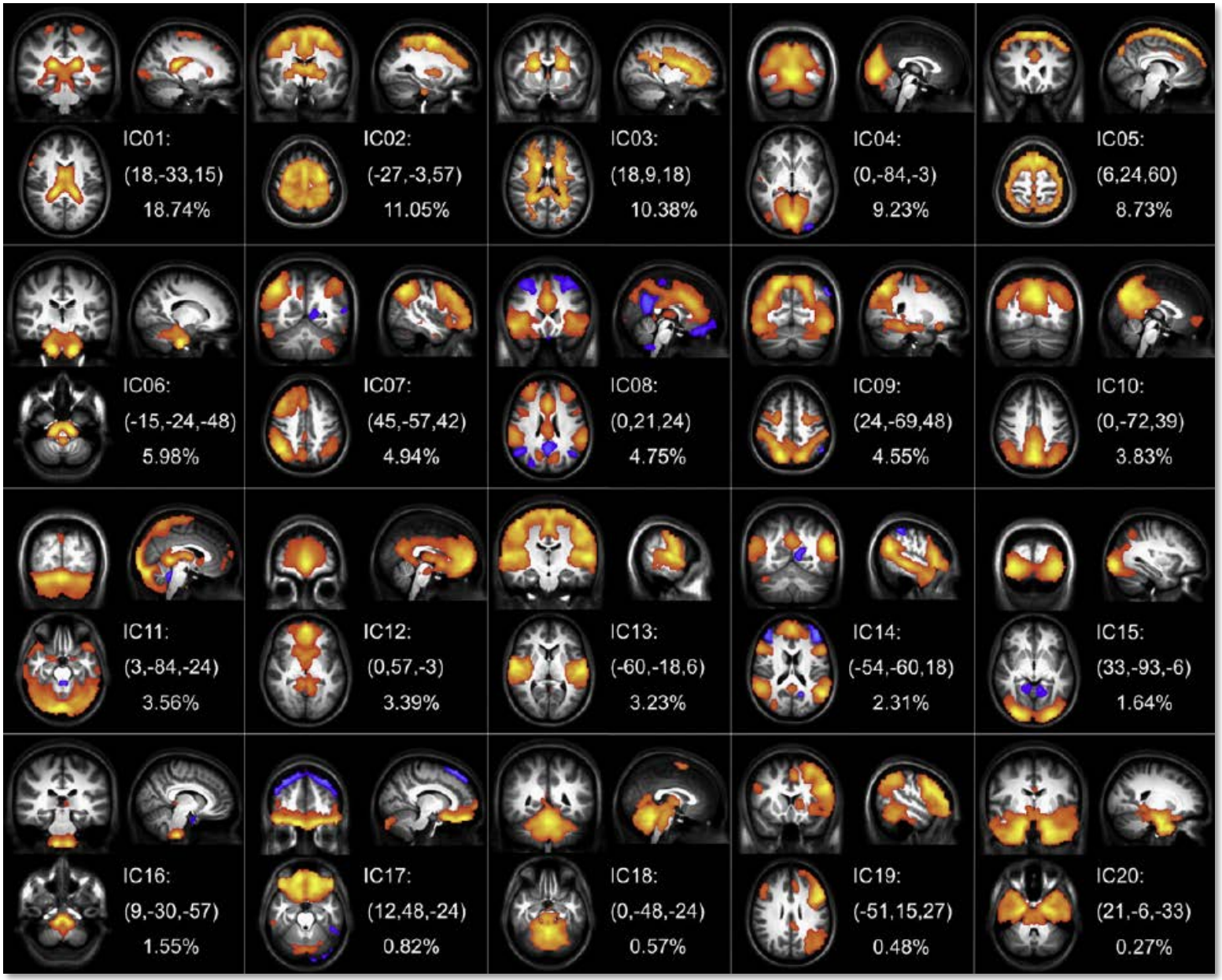
SINGLE SUBJECT

MULTI SUBJECT



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

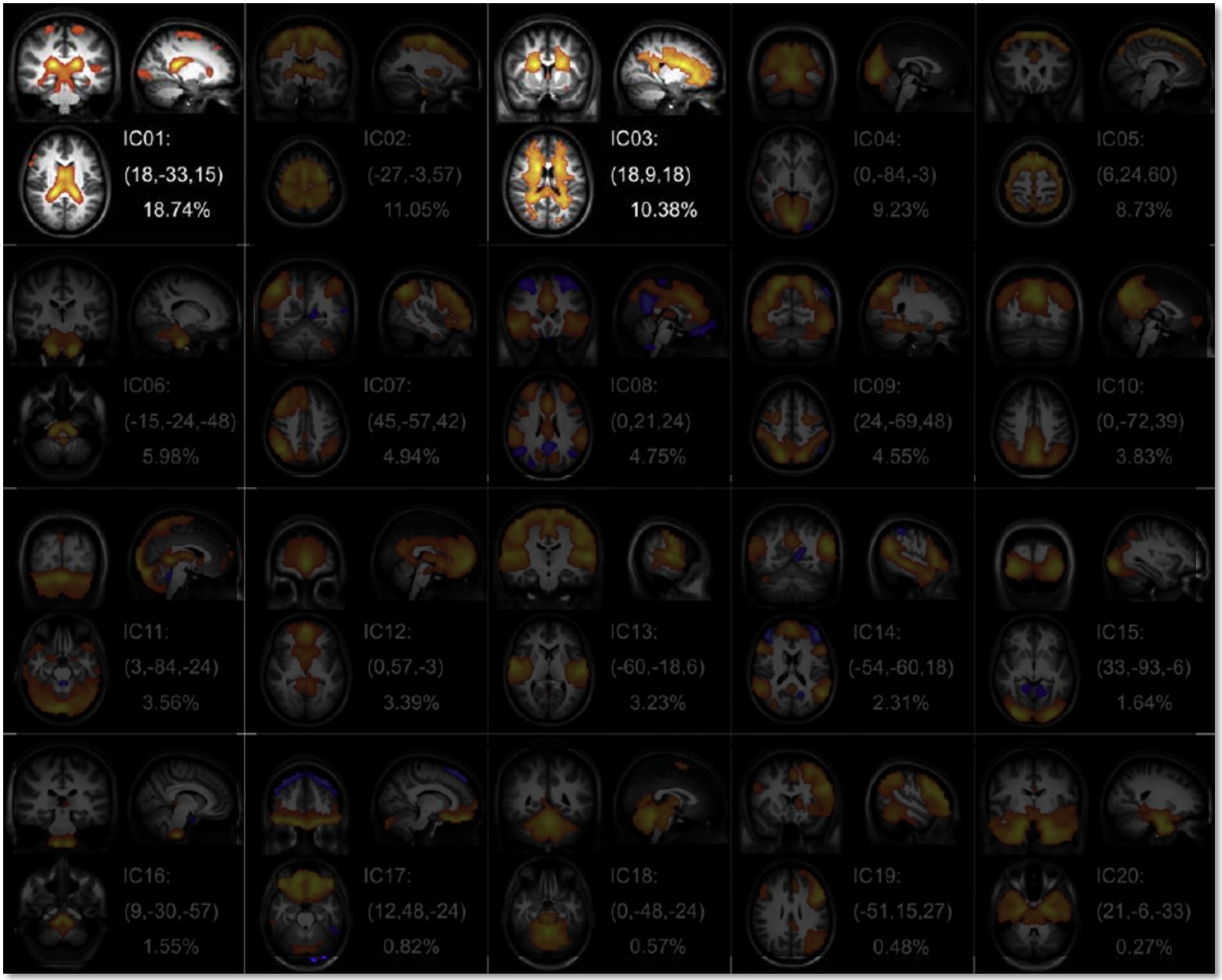
GIFT: http://mialab.mrn.org/software/ Calhoun et al., 2001



Zou et al., 2010

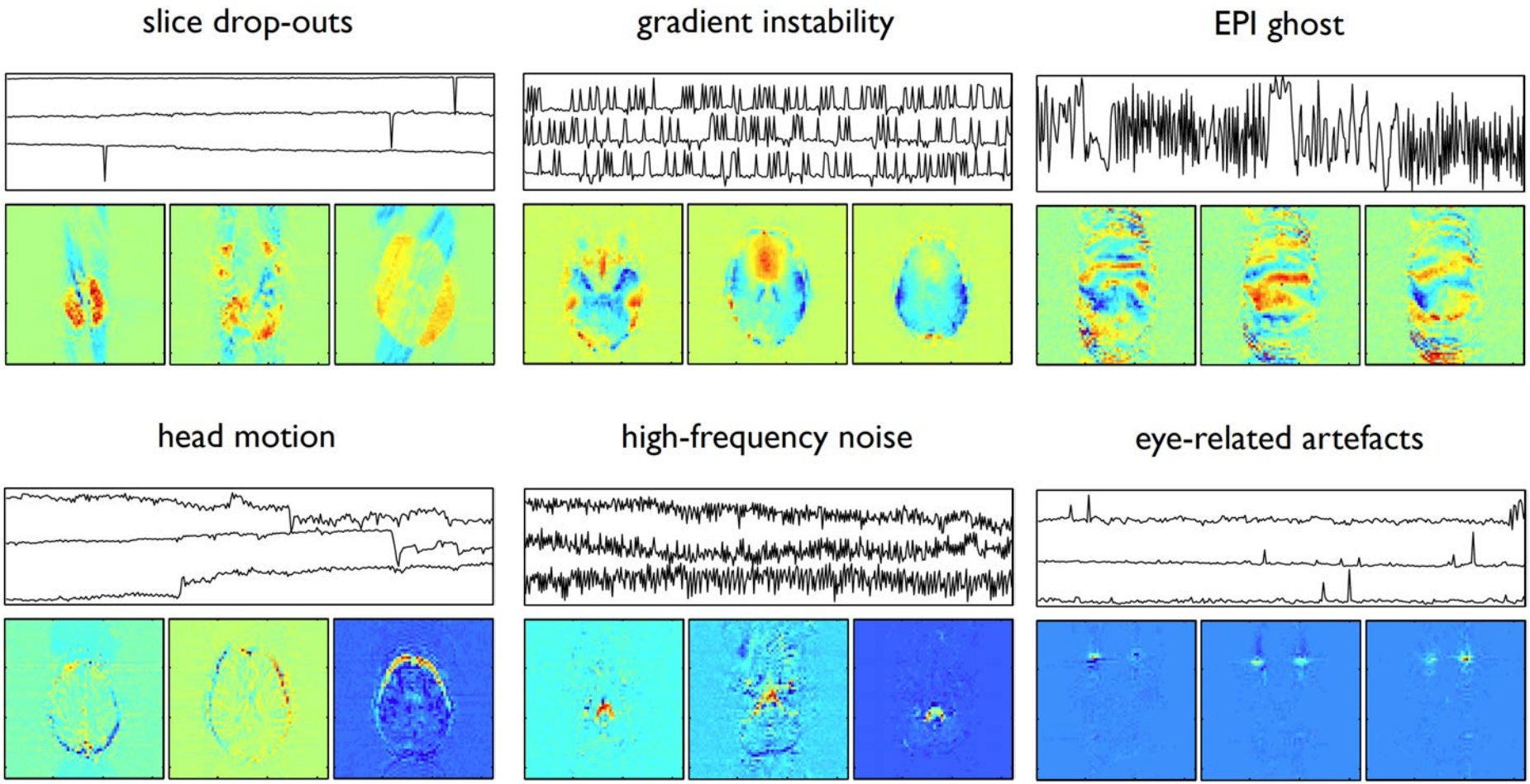
Zou et al., 2010

Zou et al., 2010



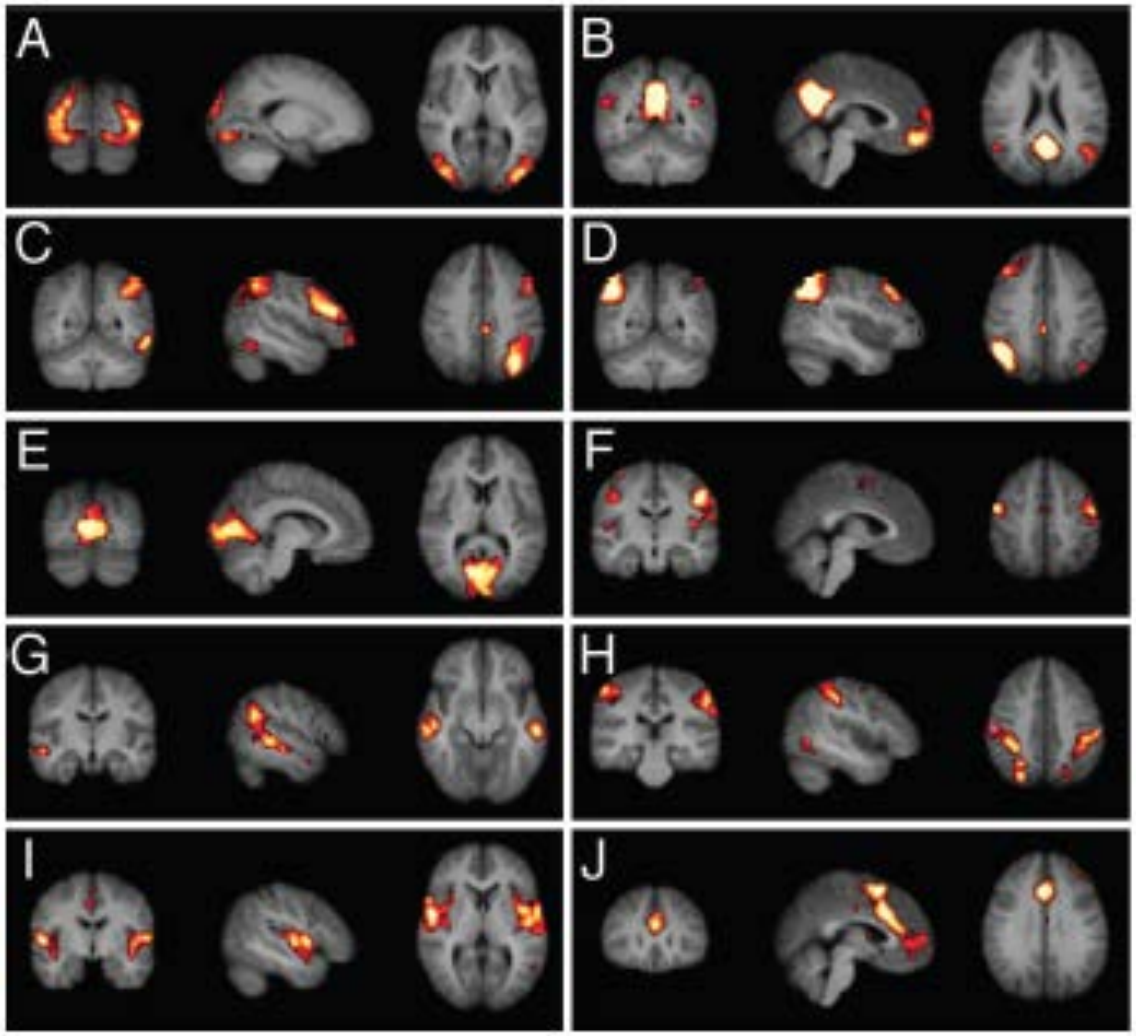
Zou et al., 2010

Noise components



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

J Neurophysiol 103: 297–321, 2010.
First published November 4, 2009; doi:10.1152/jn.00783.2009.

Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization

Koene R. A. Van Dijk,[1,2,3] Trey Hedden,[1,2] Archana Venkataraman,[4] Karleyton C. Evans,[5] Sara W. Lazar,[5] and Randy L. Buckner[1,2,5,6]

- 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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NeuroImage 59 (2012) 431–438

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

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,*]

NeuroImage 59 (2012) 2142–2154

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

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]

NeuroImage 60 (2012) 623–632

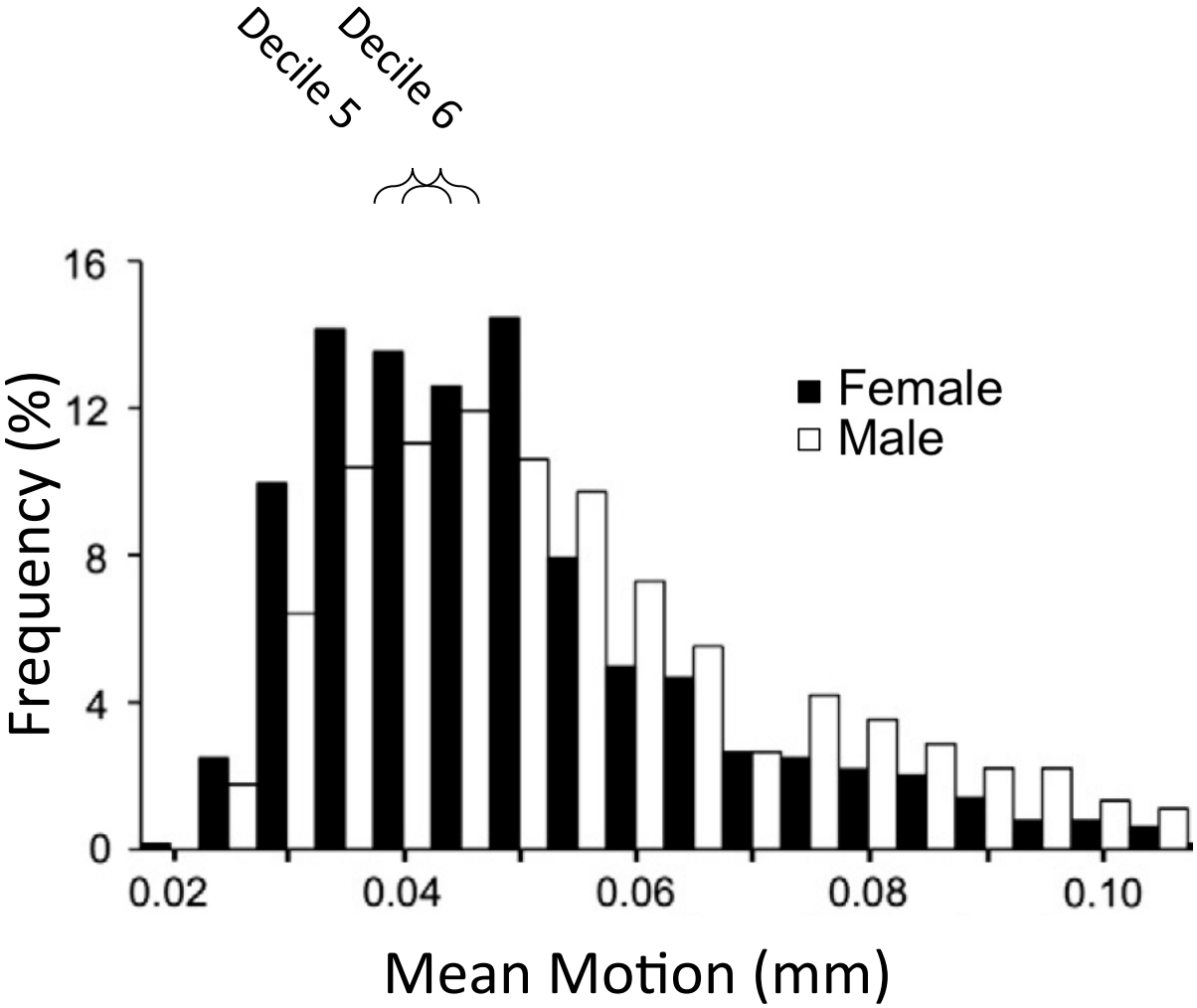
Contents lists available at SciVerse ScienceDirect

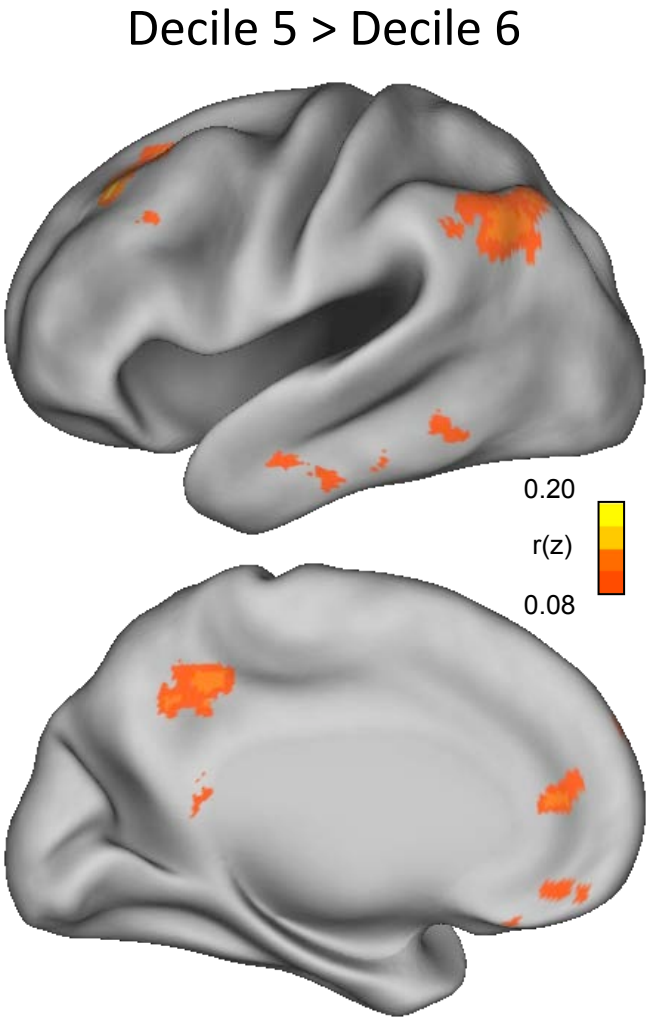
NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth ☆

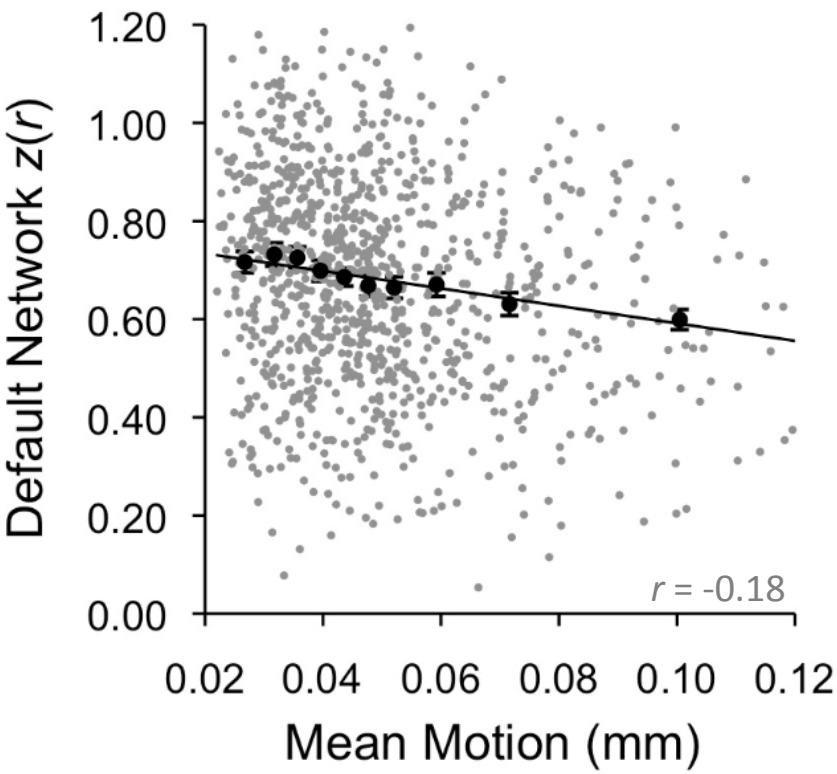
Theodore D. Satterthwaite [a,*], Daniel H. Wolf [a], James Loughead [a], Kosha Ruparel [a], Mark A. Elliott [b], Hakon Hakonarson [c], Ruben C. Gur [a,b,d], Raquel E. Gur [a,d]

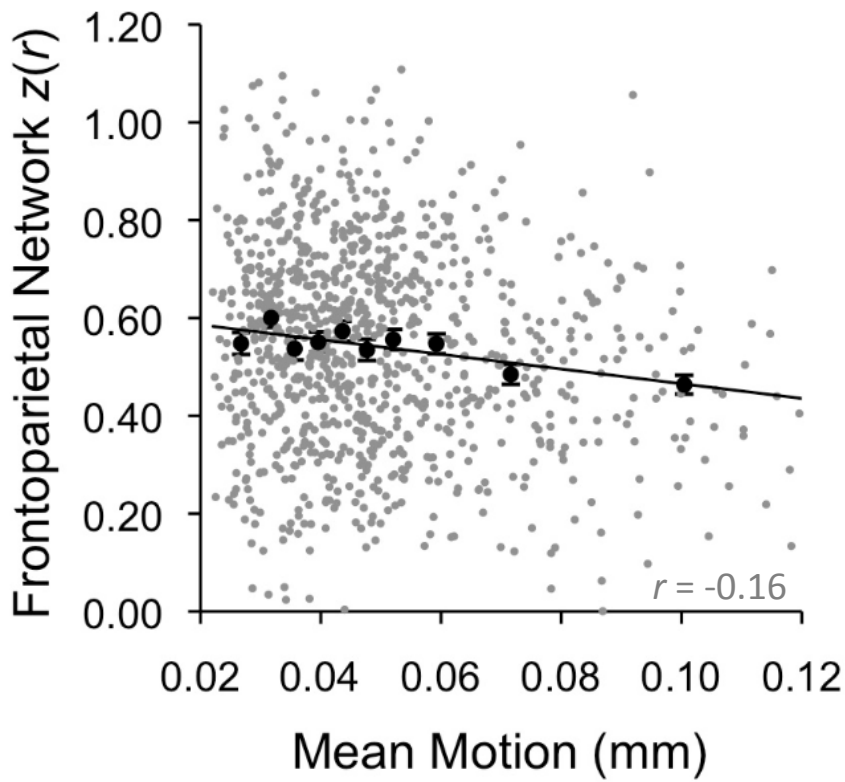




(Van Dijk et al., NeuroImage 2012)

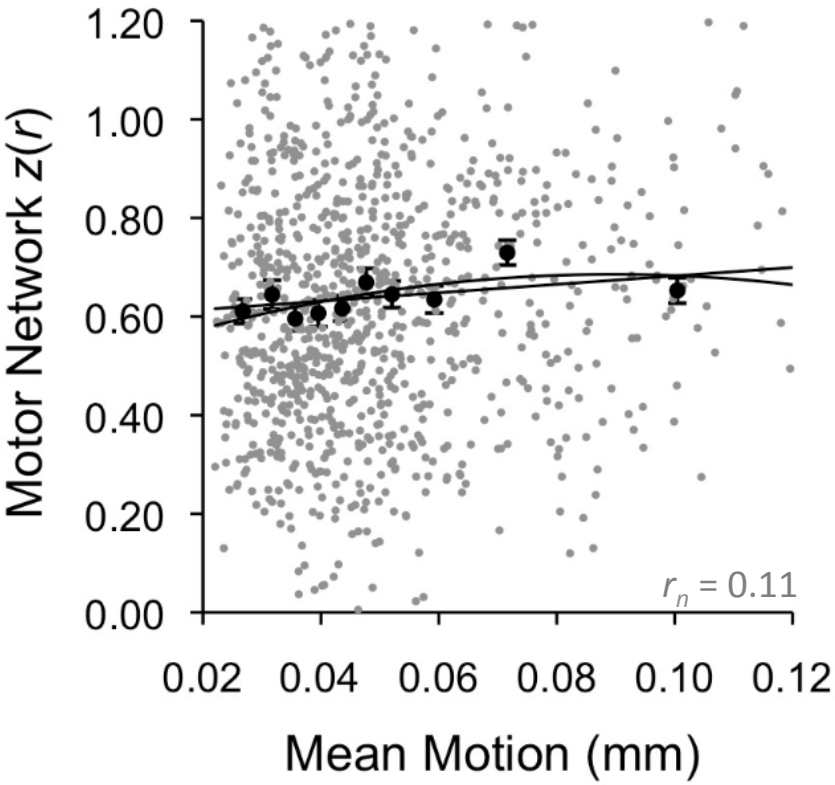
Motion decreases correlation strength in large-scale networks

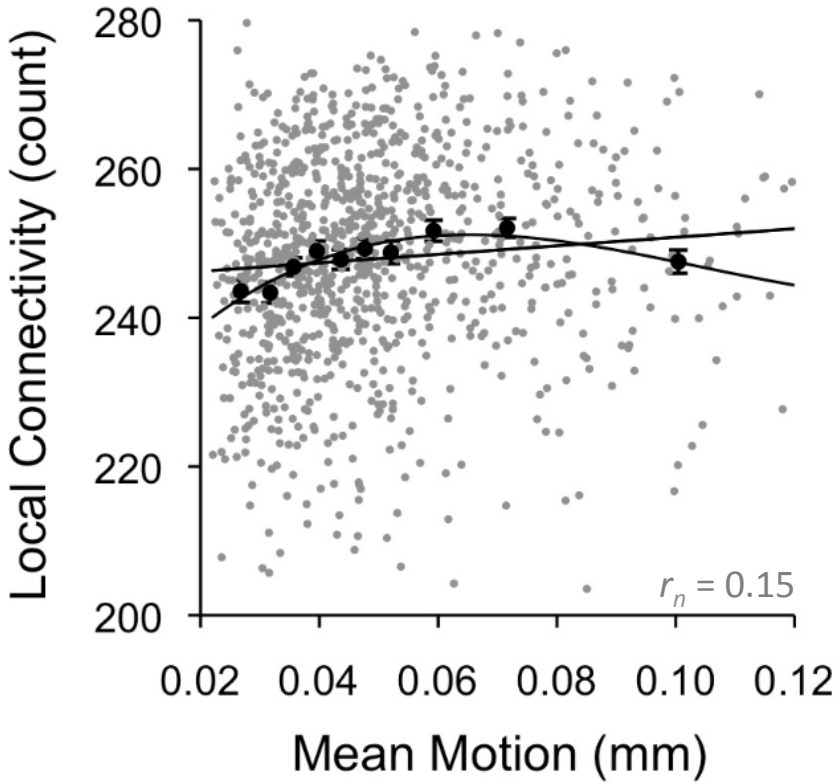




(Van Dijk et al., NeuroImage 2012)

Motion increases local functional coupling





(Van Dijk et al., NeuroImage 2012)

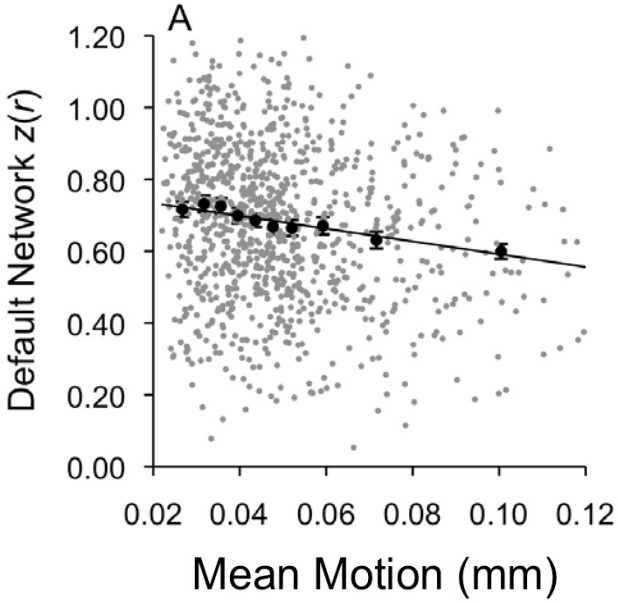
Interim conclusions

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 confortable 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.

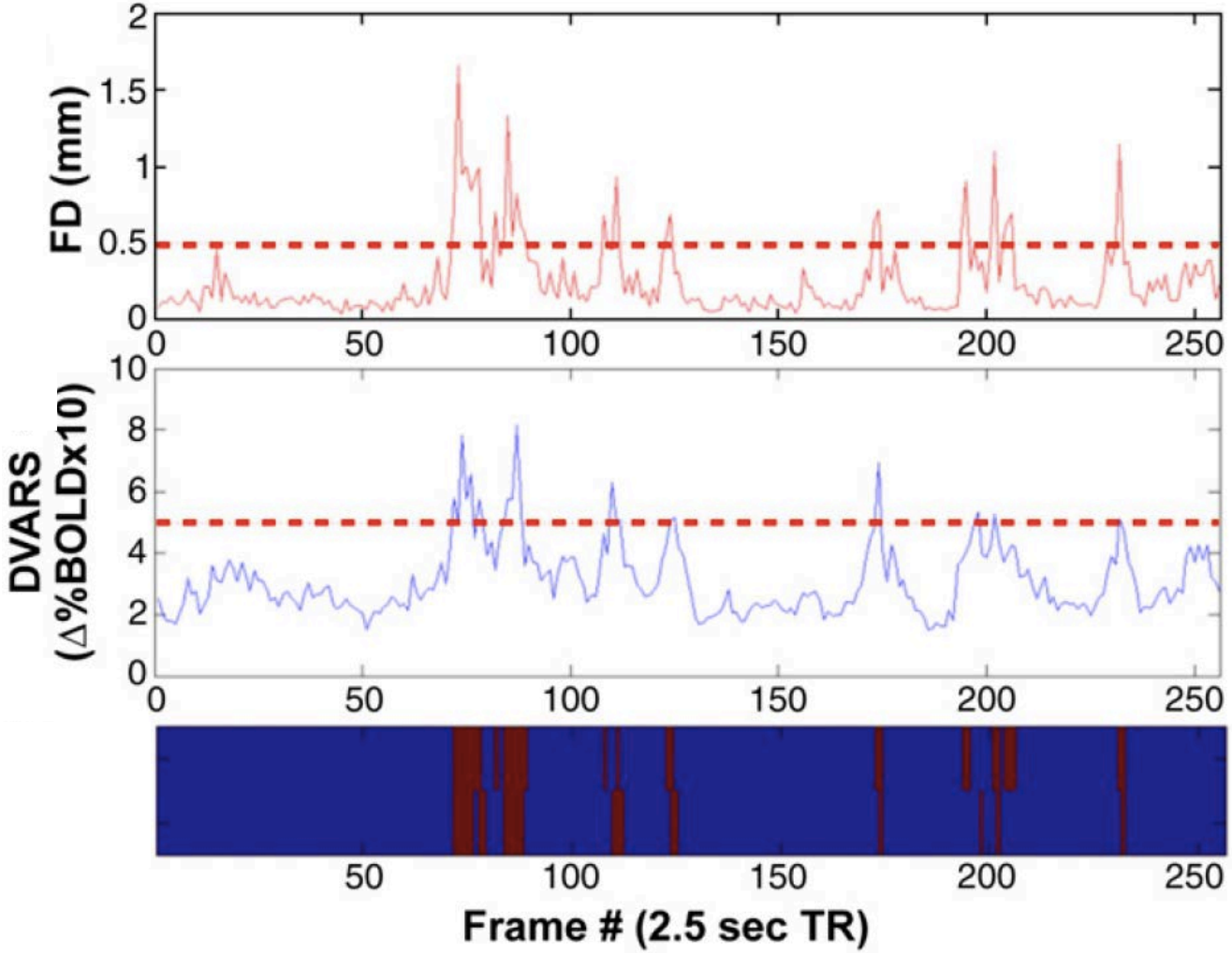
- Taking an extra minute to have the subject think by themselves if they are as confortable as possible and make any adjustment to pillows, blankets, mirror, pads, etc.

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”



(Power et al., NeuroImage 2012; 2014)

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)

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YNIMG-12041; No. of pages: 11; 4C: 6, 7, 8

NeuroImage xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

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Q1 ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data

Q2 Raimon H.R. Pruim [a,b,*], Maarten Mennes [a,b], Daan van Rooij [b,c], Alberto Llera [b], Jan K. Buitelaar [a,b,d], Christian F. Beckmann [a,b,e]

[a] Radboudumc, Donders Institute for Brain, Cognition and Behaviour, Department of Cognitive Neuroscience, Nijmegen, The Netherlands
[b] Radboud University, Donders Institute for Brain, Cognition and Behavior, Centre for Cognitive Neuroimaging, Nijmegen, The Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Psychiatry, Groningen, The Netherlands
[d] Karakter Child and Adolescent Psychiatry University Center, Nijmegen, The Netherlands
[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)

*IC-label	Initial ICA results		After ICA-AROMA	
	Mean ± SD number ICs	Correlation with RMS-FD (p-value)	Mean ± SD number ICs	Correlation with RMS-FD (p-value)
Motion	12.4 ± 5.7	0.87 (<1e-9)	0.9 ± 0.8	0.31 (0.10)
RSN	8.0 ± 2.7	−0.06 (0.76)	7.7 ± 2.8	−0.07 (0.71)
Other	14.2 ± 4.7	0.43 (0.02)	2.8 ± 2.1	0.40 (0.03)
Total	34.5 ± 8.2	0.83 (<1e-7)	11.4 ± 3.2	0.29 (0.12)

(Pruim et al., NeuroImage 2015)

How to minimize confounding effects of head motion (2)

4. Prospectively correct for motion during data acquisition *(Thesen et al., 2000; Ward et al., 2000, Tisdall et al., 2013)*

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

6. Regress motion estimates from between-subject analyses

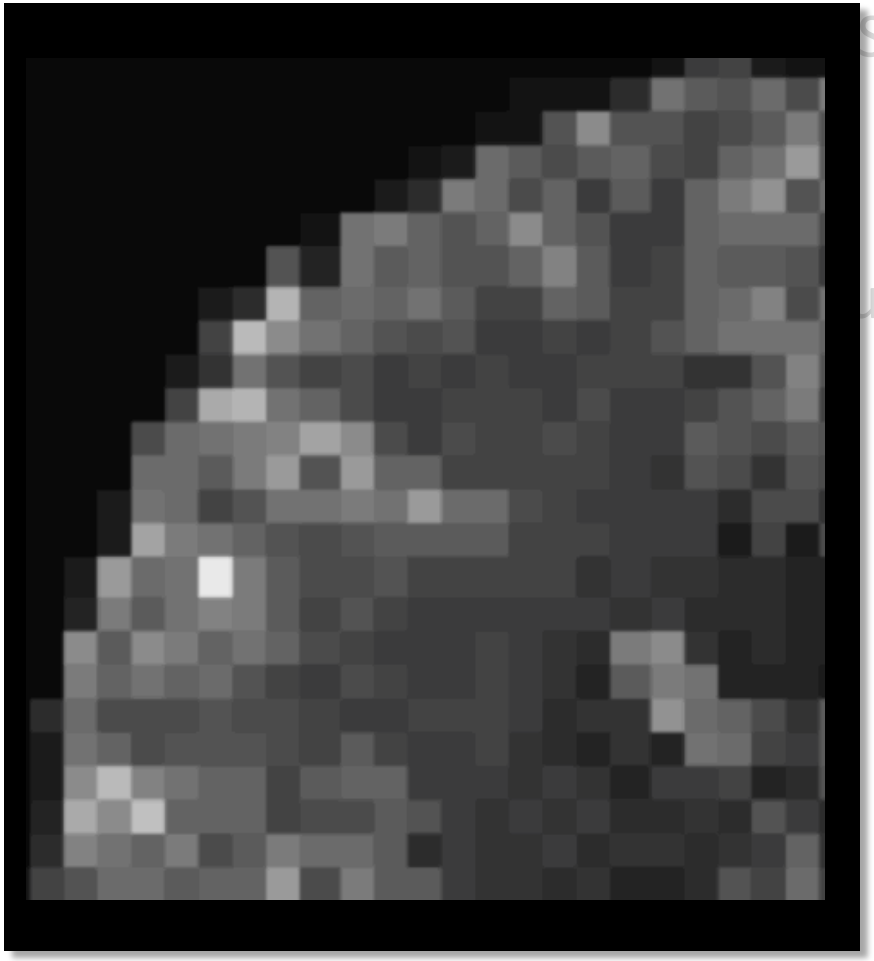
7. Match the level of motion between subject groups

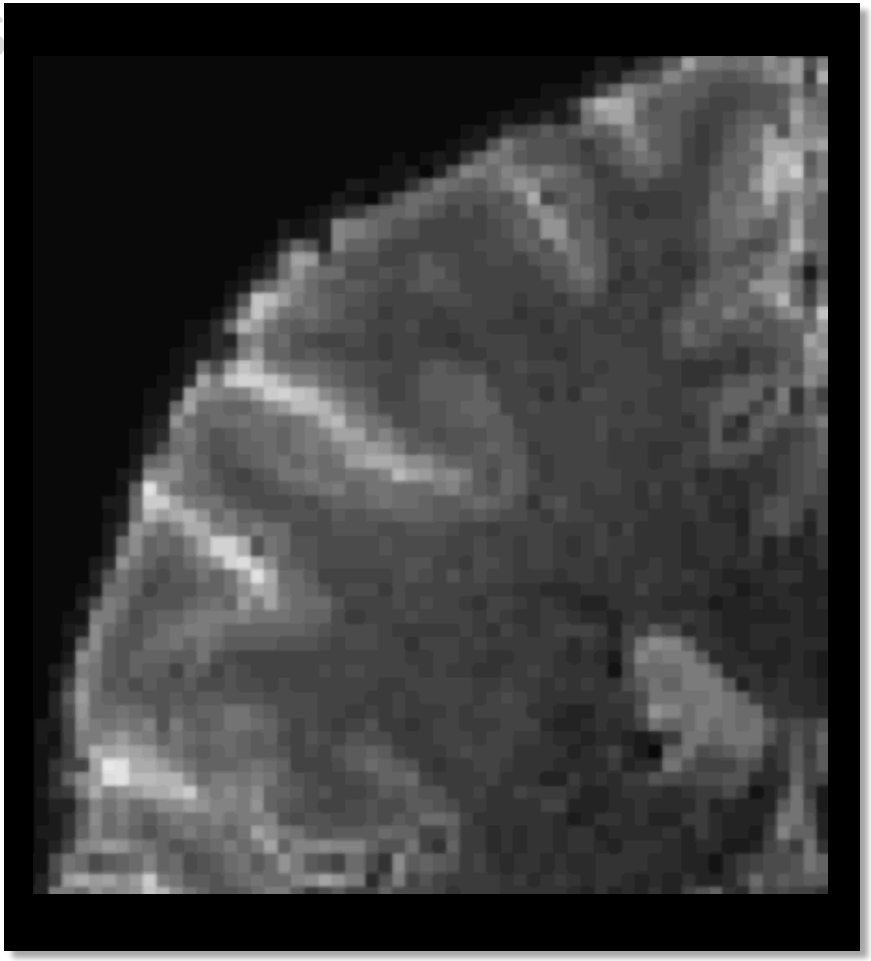
- Methods:
  - Seed based analysis
    - Removal of physiological noise
  - Independent component analysis (ICA)
  - Confounding effects of head motion

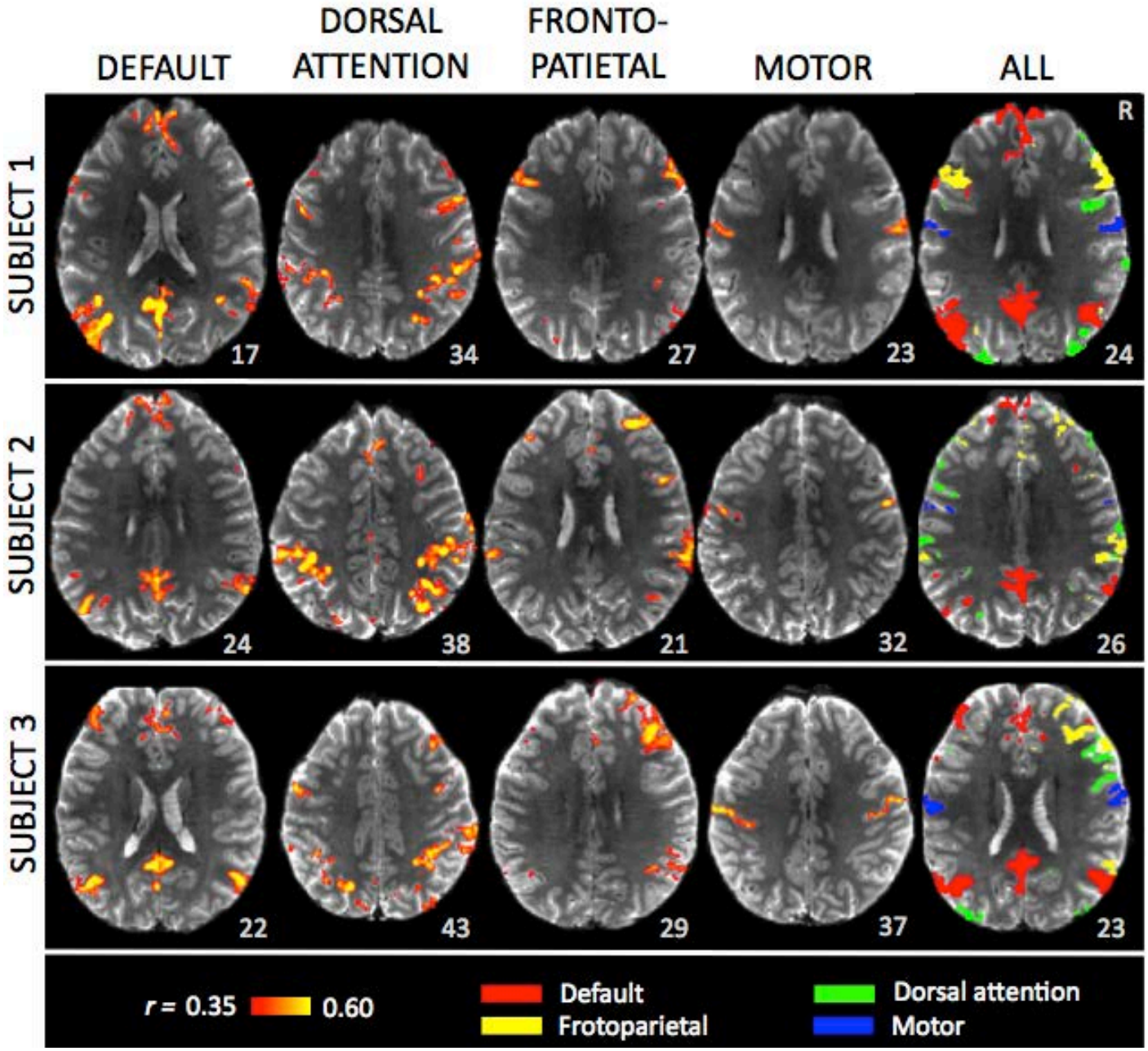
- Future directions
  - Higher field strength offers higher spatial resolution
  - Simultaneous Multi-Slice (SMS) acquisition offers higher temporal resolution

Future directions

- Higher field strength offers higher spatial resolution






DEFAULT
DORSAL ATTENTION
FRONTO-PATIETAL
MOTOR
ALL
SUBJECT 1
SUBJECT 2
SUBJECT 3
R
17
34
27
23
24
24
38
21
32
26
22
43
29
37
23
r = 0.35
0.60
Default
Frotoparietal
Dorsal attention
Motor

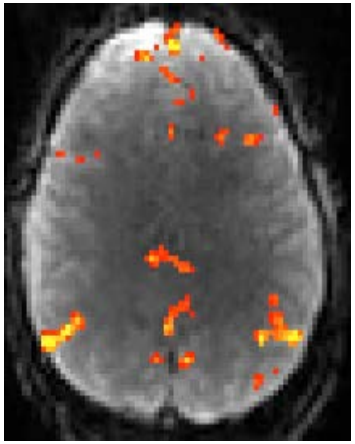
Simultaneous Multi-Slice (SMS) acquisition offers higher temporal resolution

	TR	#volumes in 6 min	spatial resolution	SMS
Standard scan	3000 ms	120	3 mm	-
SMS scan	350 ms	~1000	2.5 mm	12

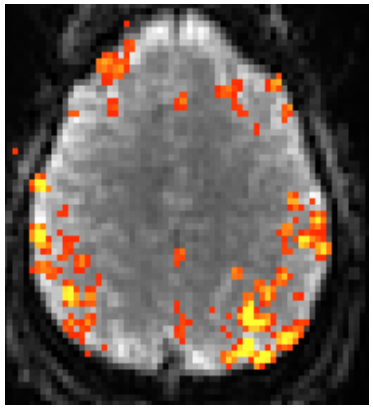
Kawin Setsompop, Jonathan Polimeni

Simultaneous Multi-Slice (SMS) acquisition offers higher temporal resolution

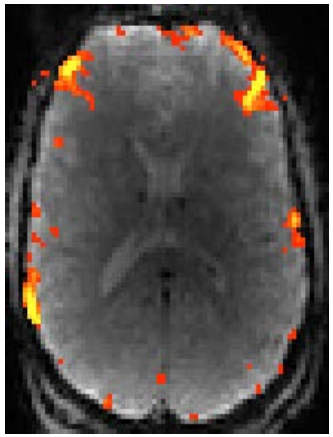
Default Mode Network



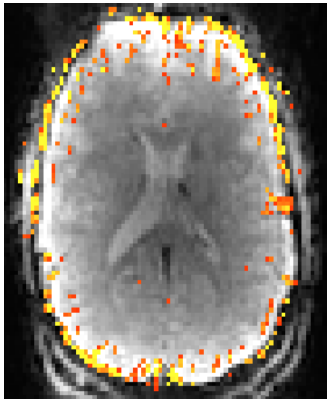
Dorsal Attention System



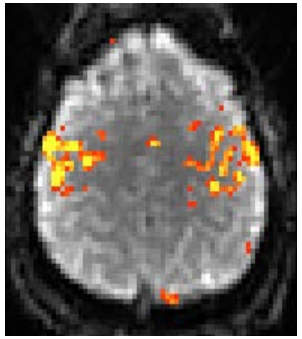
Fronto-parietal Control Network



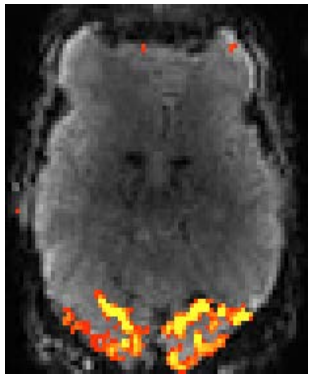
Noise

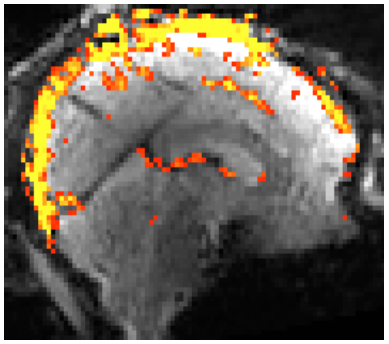


Motor Network



Visual Network





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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

- **Van Dijk KRA** et al. *The influence of head motion on intrinsic functional connectivity MRI*. Neuroimage. 2012; 59(1):431-8. http://nmr.mgh.harvard.edu/~kdijk/PDF/Van_Dijk_et_al_2012_Neuroimage.pdf

- **Power et al.** *Methods to detect, characterize, and remove motion artifact in resting state fMRI*. Neuroimage. 2014; 84:320-41.

- **Pruim RH et al.,** ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage. 2015 Mar 11. pii: S1053-8119(15)00182-2.

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