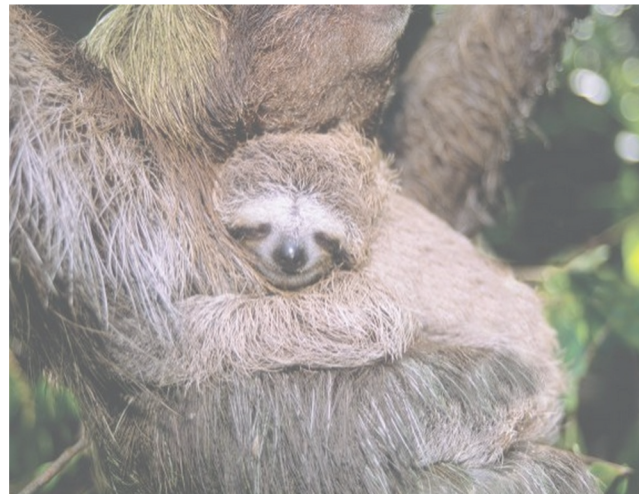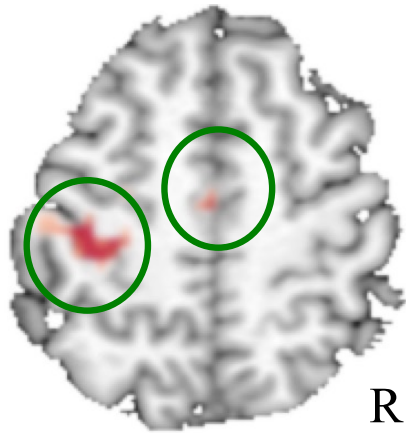# Resting State fMRI
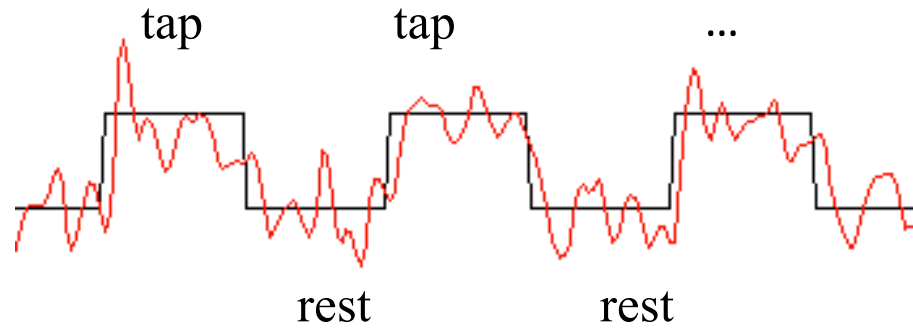
Catie Chang
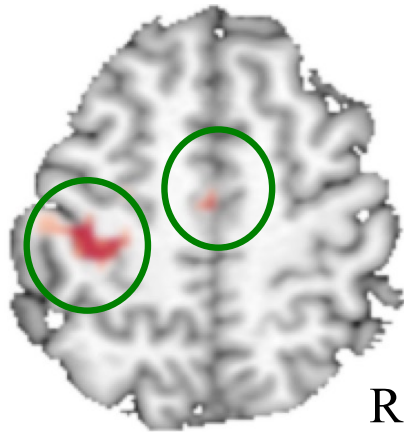Research Fellow, AMRI / NINDS / NIH
fMRI Summer Course * 2017

Outline

- **Background & motivation**
- Analyzing resting-state data
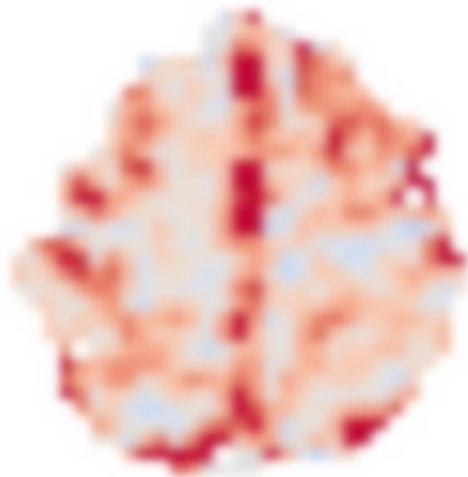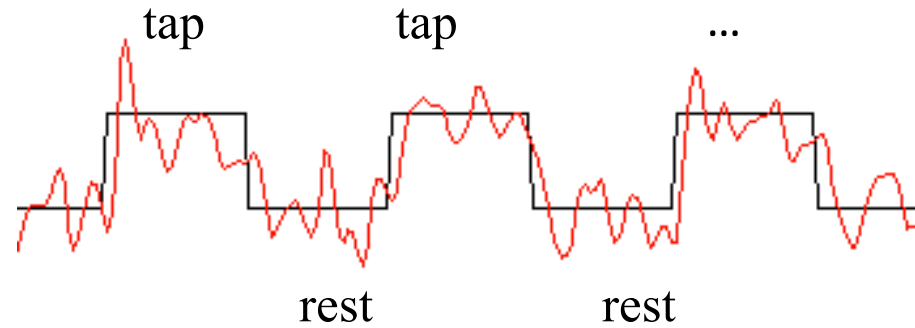- Issues, caveats, and interpretation
- Directions

Right-hand fingertapping task

tap   tap   ...

rest   rest

Right-hand fingertapping task

tap   tap   ...

rest   rest
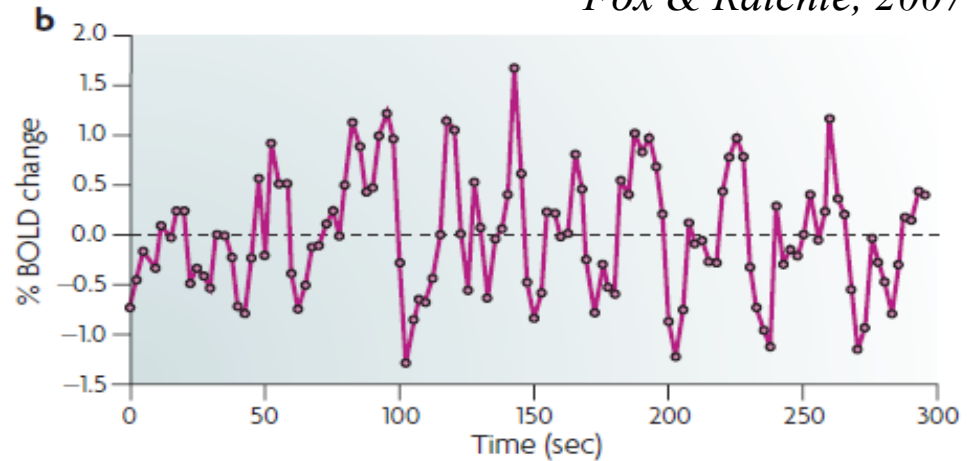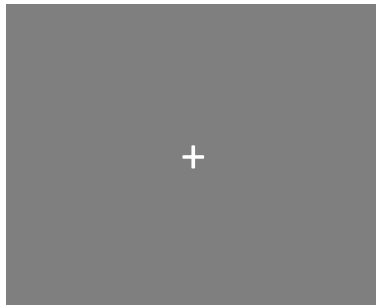
R

courtesy Jen Evans

% signal change

1.0

-1.0

"spontaneous brain activity"
- that which cannot be attributed to experimental task/stimuli
- accounts for most of the brain's energy consumption
- what can we learn by studying it?

+

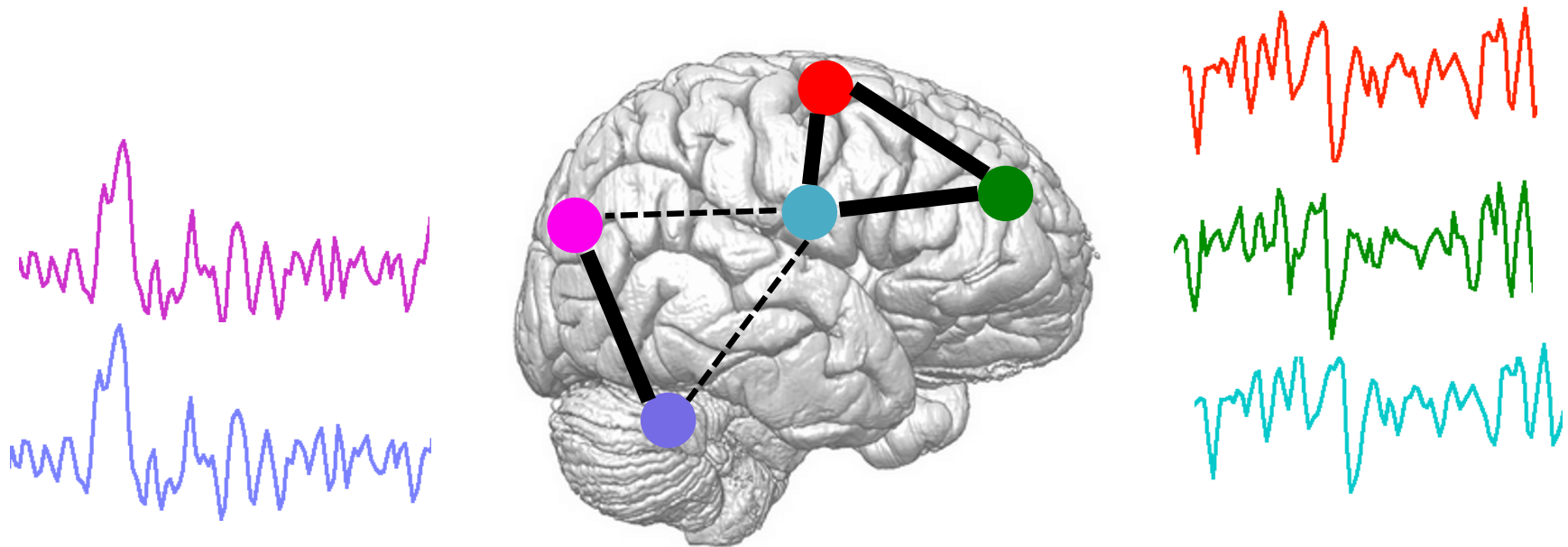- instructions ~ "keep eyes closed" or "keep eyes open and fixate"
- usually 5-15 minutes long

Fox & Raichle, 2007

How to analyze the data?
? no (known) conditions to compare
? no idea what the subject is thinking/feeling
? how to separate "signal" from "noise"

"Functional connectivity"

- FC: statistical dependence (e.g. correlation) between the time courses of different brain regions
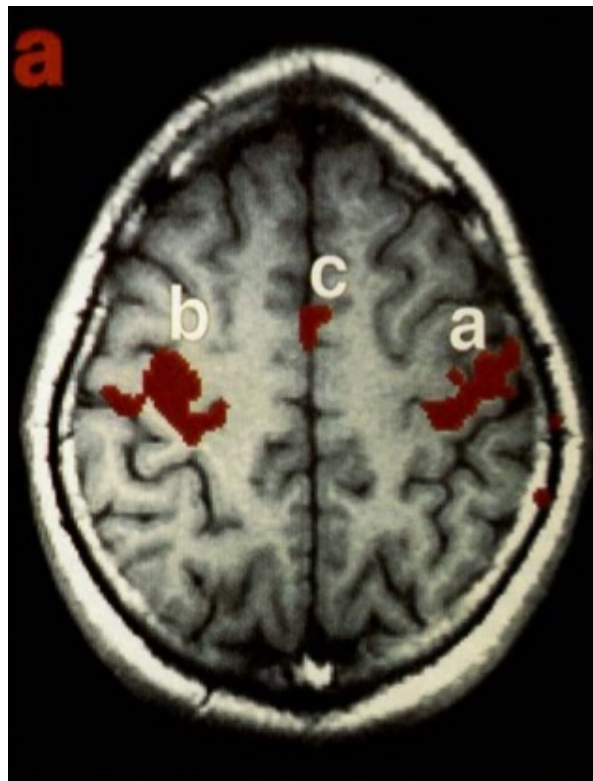- suggests "network" interactions, though interpretation is complicated

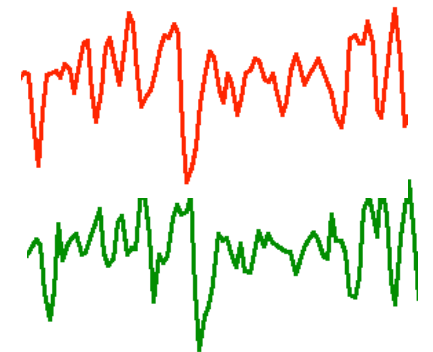# Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI

Bharat Biswal, F. Zerrin Yetkin, Victor M. Haughton, James S. Hyde

Mag. Res. Med. 1995,   ~5300 citations

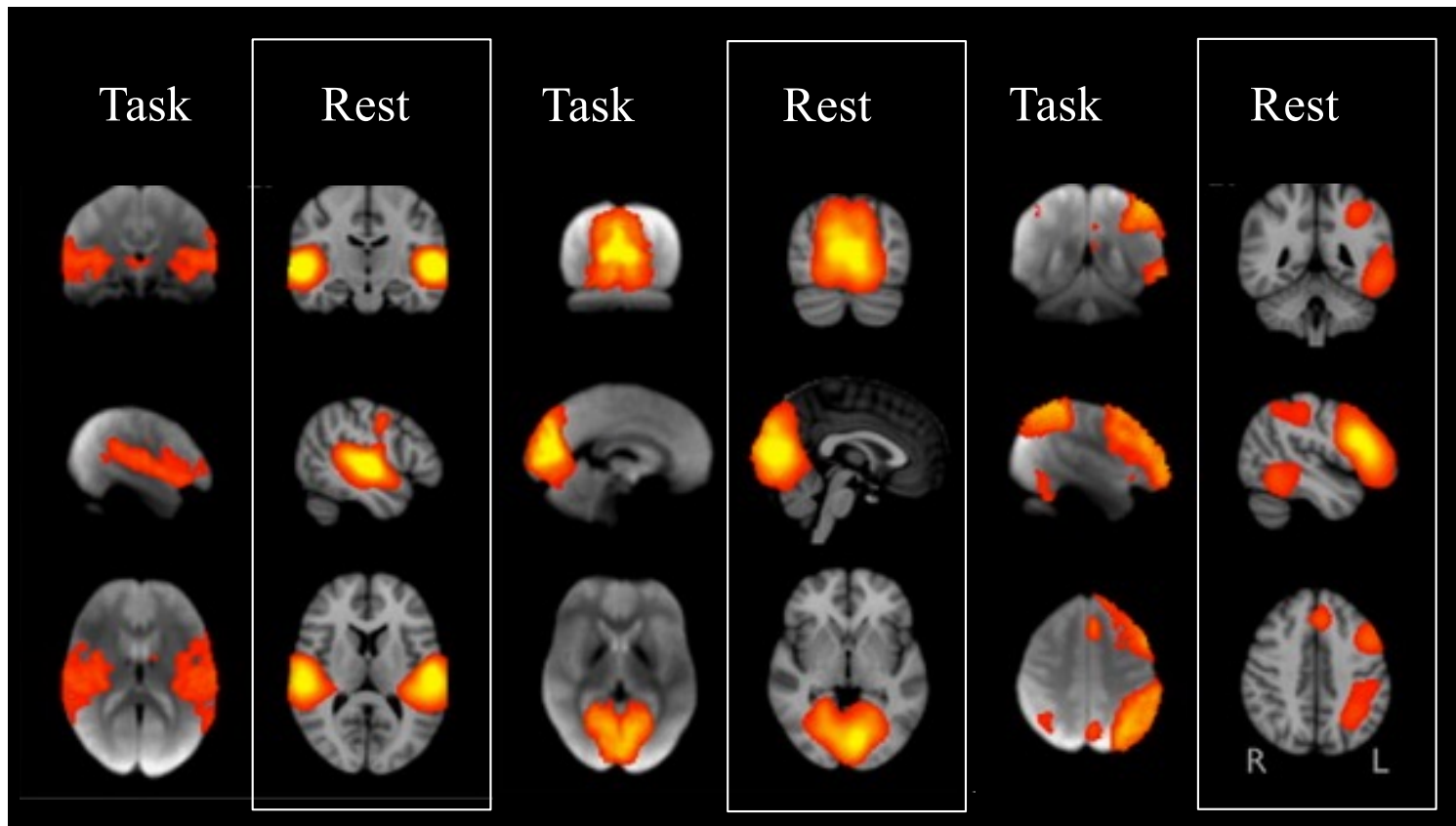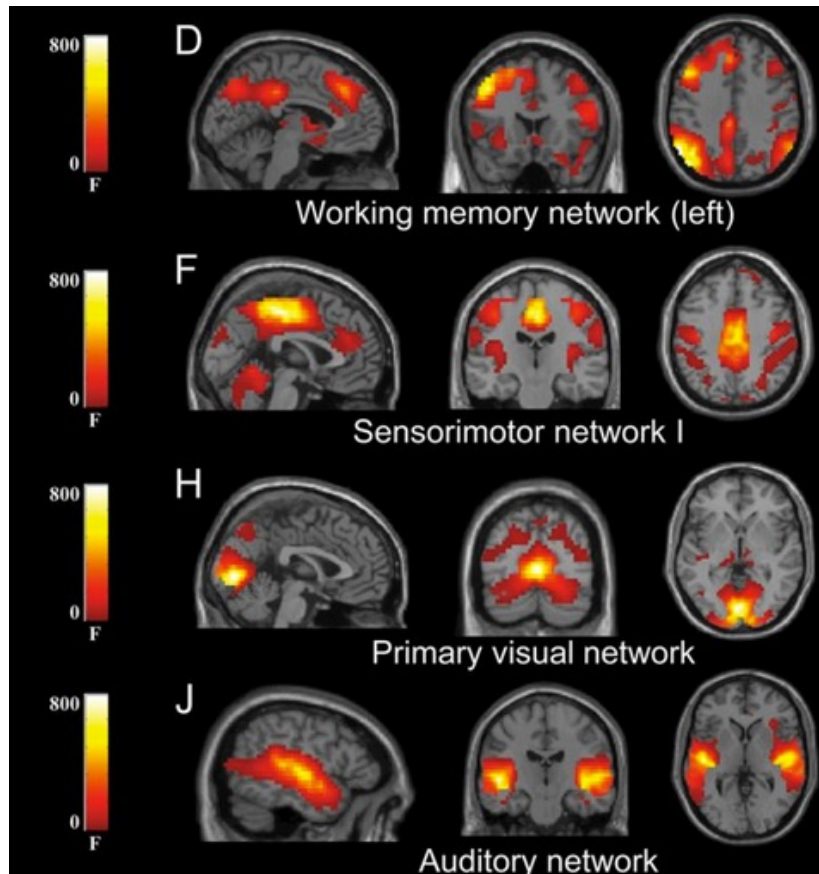task *activation*   resting state *correlation*

Resting-state "networks" closely resemble task-activated networks

Smith et al, 2009

-> Suggests we may be able to map multiple functional networks without needing tasks
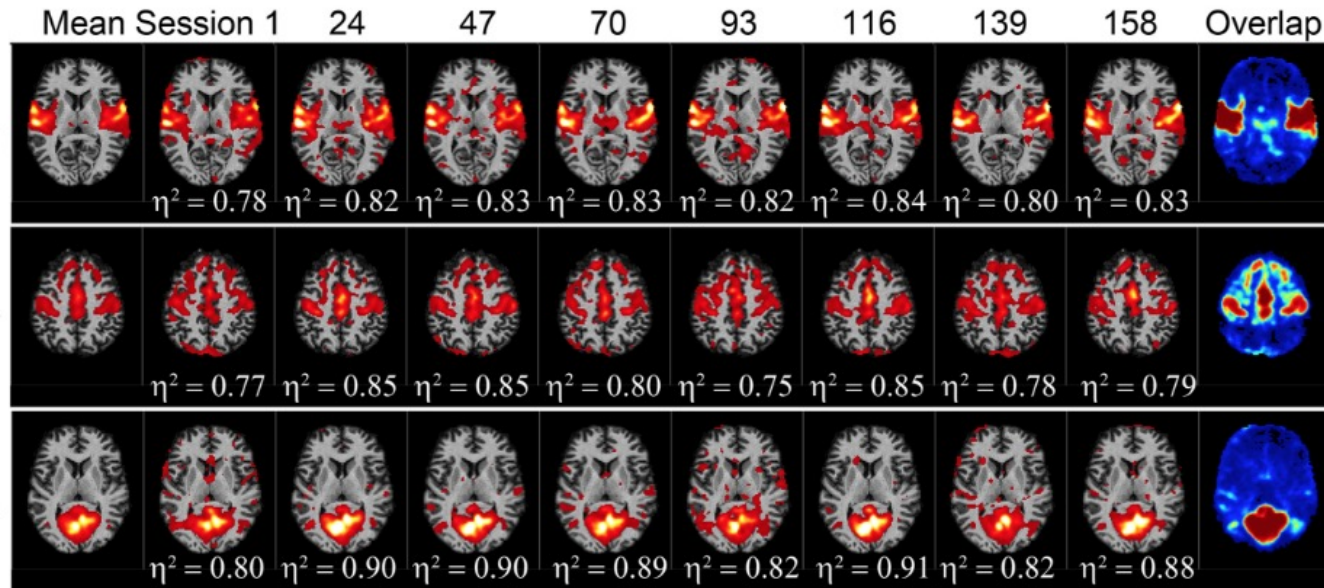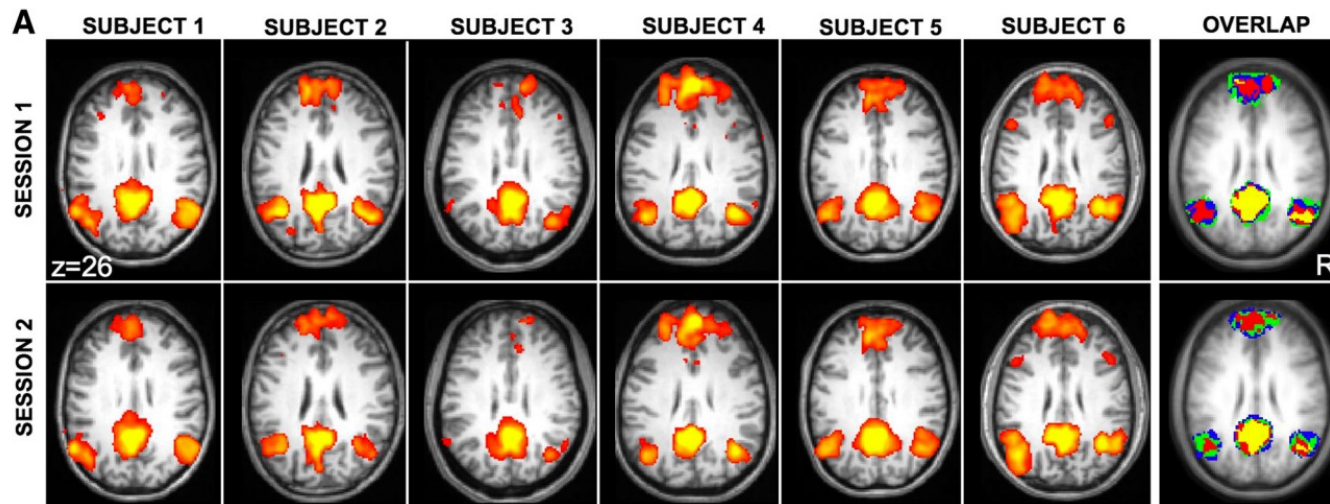
"Resting-state networks"

Working memory network (left)

Sensorimotor network I

Primary visual network

Auditory network

Rocca et a. 2012

- **Resting-state network** : set of regions ("nodes") with mutually high functional connectivity in resting state
  - approx 10-15 reliable patterns at this spatial granularity
  - often named after the functional areas with which they overlap

- Fixed # of networks?
  - FC can be studied at multiple scales (spatial and temporal)

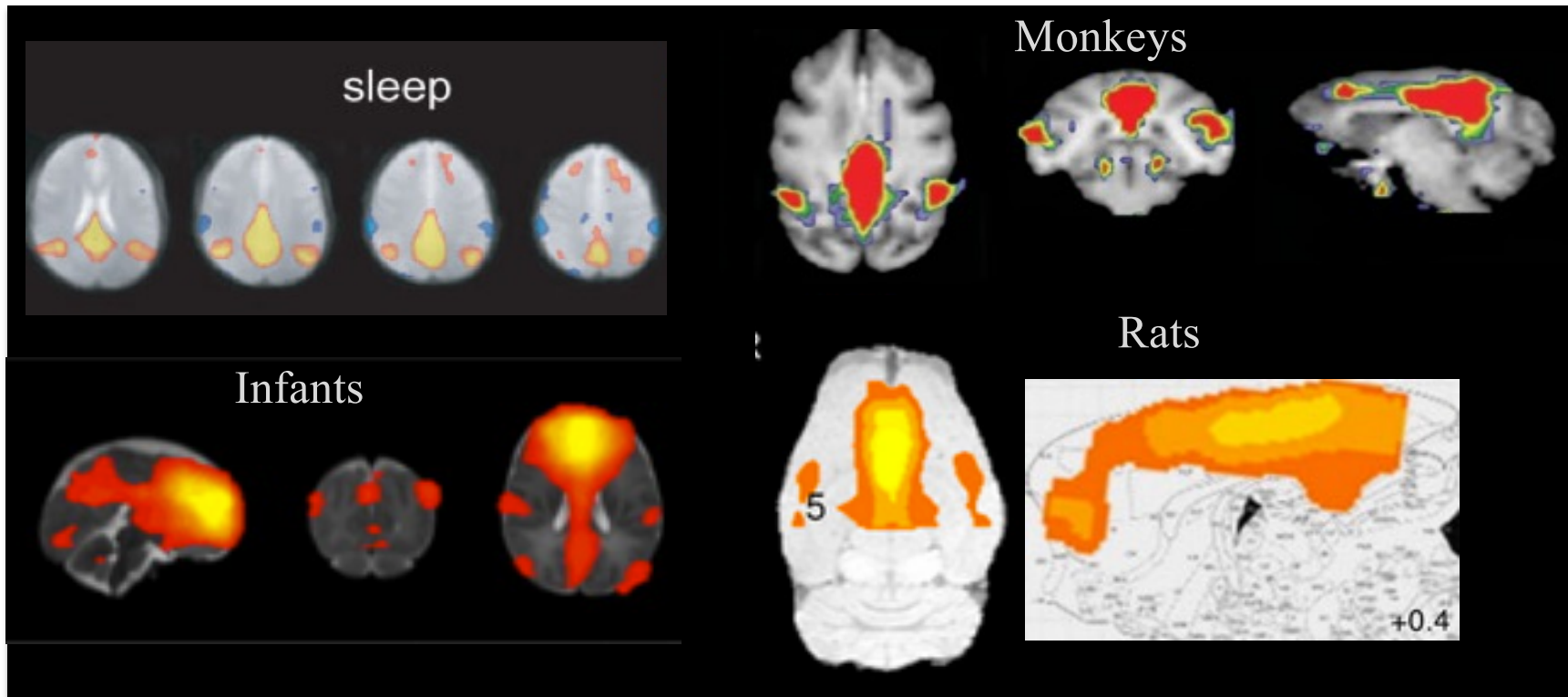# Reliability of resting-state networks

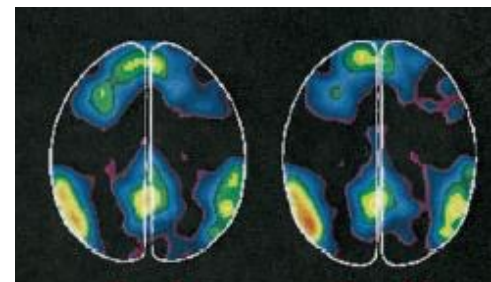*Choe et al, 2015*

Van Dijk et al. 2010

Reliability of resting-state networks

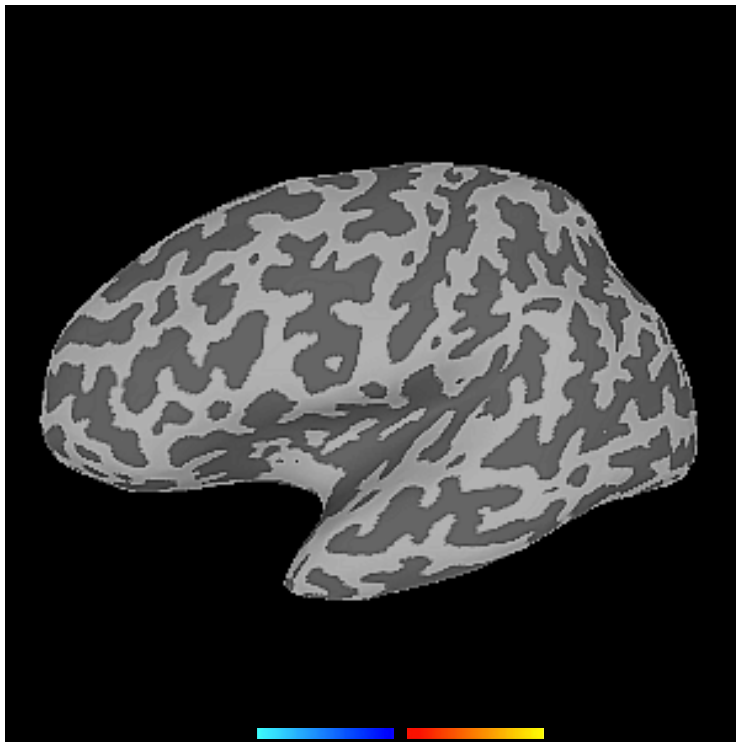*Horovitz et al. 2008; Doria et al. 2010; Vincent et al. 2007; Lu et al. 2007*

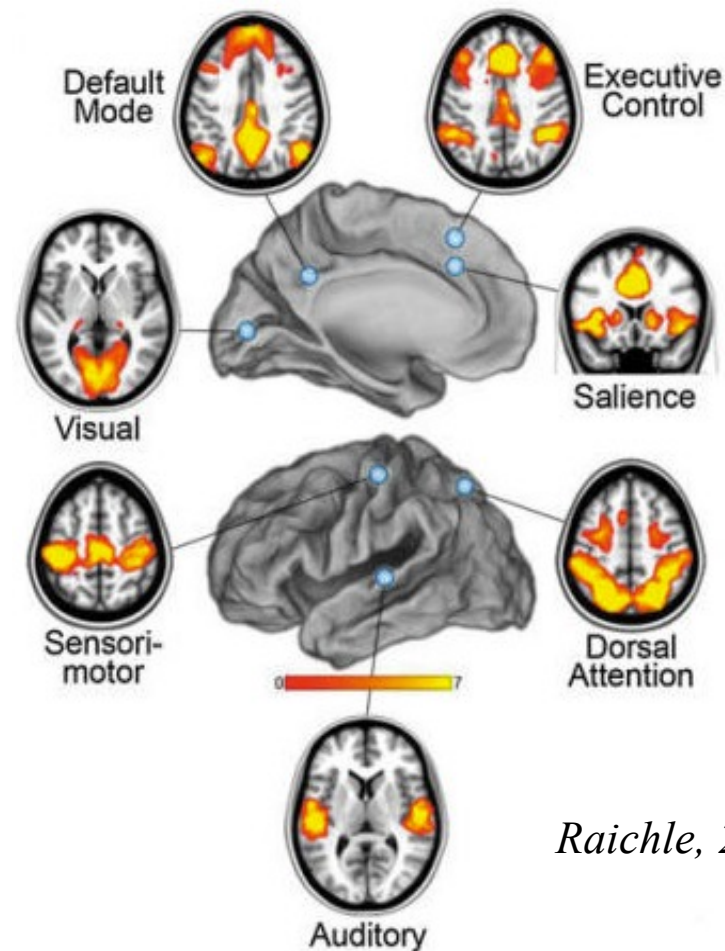**Default-mode network**

Raichle at el., 2001->
Greicius at el., 2003

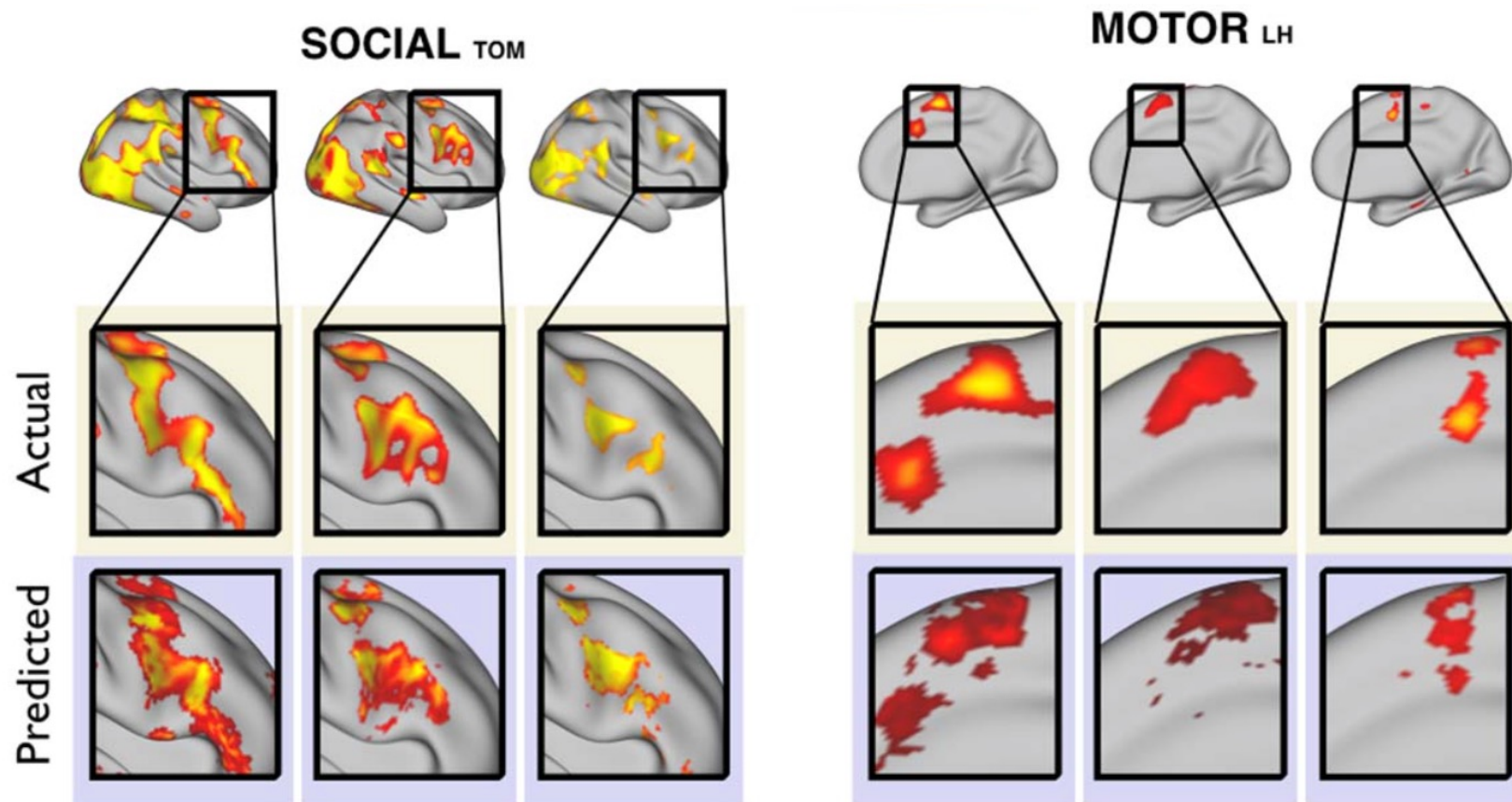# Resting-state data appears to provide info about functional brain organization
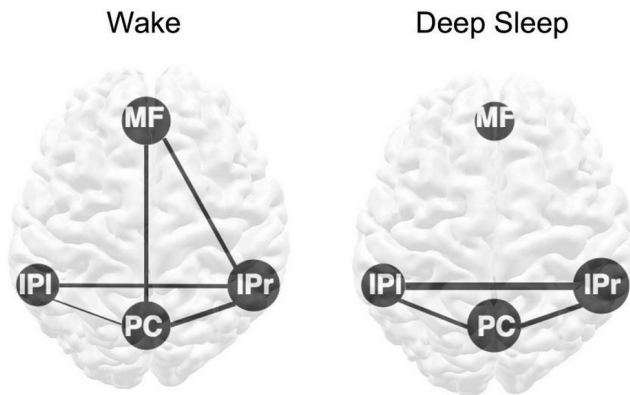

courtesy Zhongming Liu

Raichle, 2011

Resting-state data can predict task activation
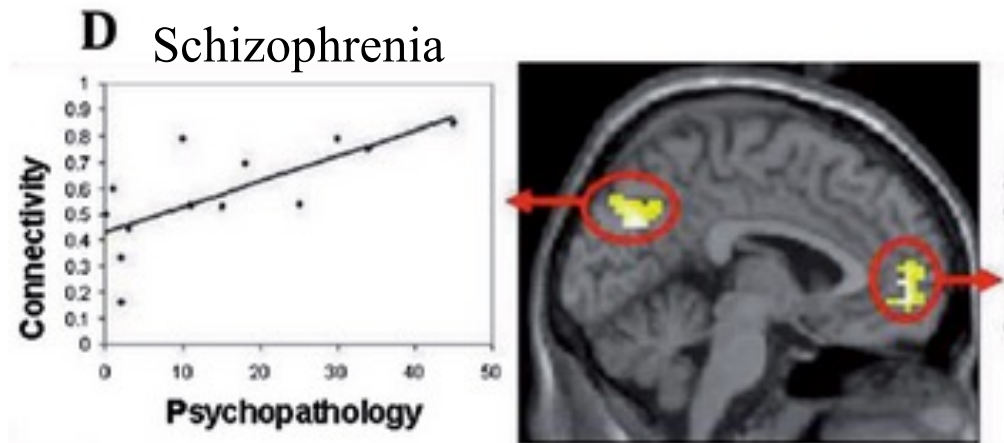

Tavor et al. 2016
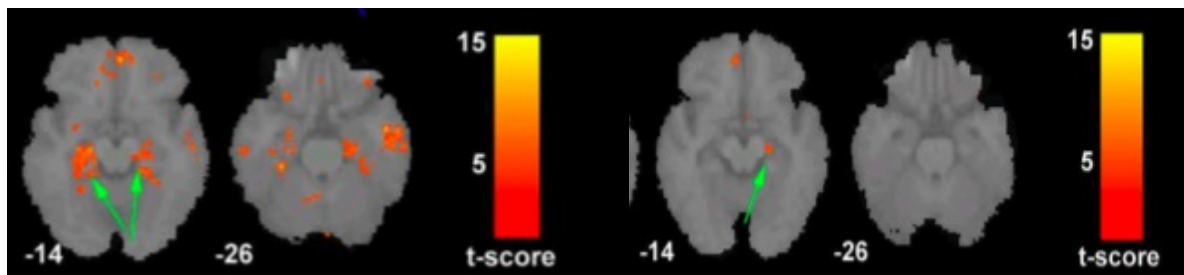
Condition-dependence of resting-state networks

Wake   Deep Sleep

Horovitz et al., 2009

Schizophrenia

Whitfield-Gabrieli et al. 2009

Healthy controls   Alzheimer's Disease

Greicius et al. 2004

Table 1. Number of publications in which iFC or resting state approaches have been used to study a variety of disorders and conditions (PubMed search on 25 January 2012)

Disorder/Condition	# studies
Schizophrenia	45
Alzheimer's Disease	44
Depression	42
Mild Cognitive Impairment (MCI)	33
Aging	39
Epilepsy	29
Substance Dependence	28
ADHD	16
Multiple Sclerosis	13
Autism	12
Parkinson's Disease	11
Pain	10
Anxiety Disorders	8
Sleep	2
Miscellaneous Neurological Disorders	10
Stroke	7
Obsessive Compulsive Disorder (OCD)	8
Posttraumatic Stress Disorder (PTSD)	8
Amnesia	4
Brain Lesions	7
Dementia	2
Seizure	3
Trauma	4
Bipolar Disorder	3
Personality Disorders	2
Cerebral Palsy	2
Fetal Alcohol Syndrome	2
Migraine	2
Psychopathy	2
Learning Disabilities	1
Tourette Syndrome	1

*Kelly et al. 2012*

Resting-state fMRI is a large & growing field

+ can derive many networks from one set of task-free data

+ no task or task compliance needed

+ tool for studying state- or disease-related differences in
   functional organization

Outline

- Background & motivation
- **Analyzing resting-state data**
  - **seed-based correlation**
  - **independent component analysis (ICA)**
  - **complex network analysis**
- Issues, caveats, and interpretation
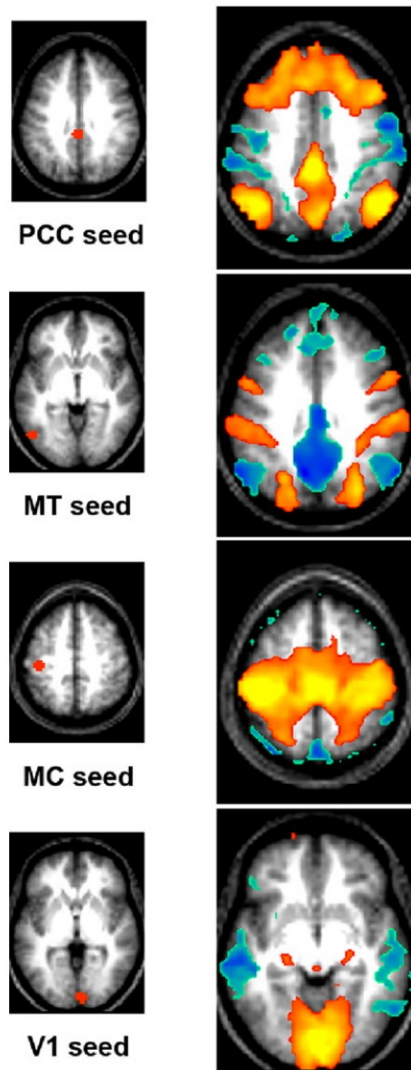- Directions

Seed-based correlation

- Which areas are most highly correlated with a region of interest ("seed")?
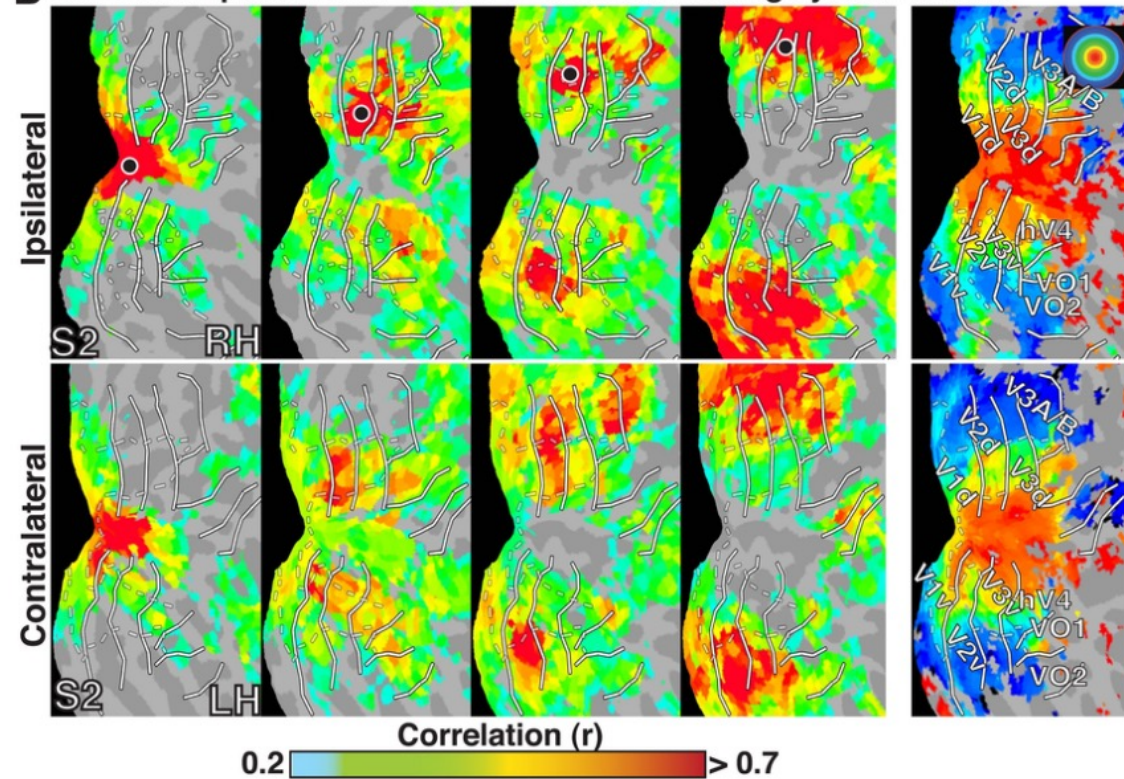- Implemented with GLM (linear regression)

seed

correlate seed's time
series with every other
voxel's time series

threshold
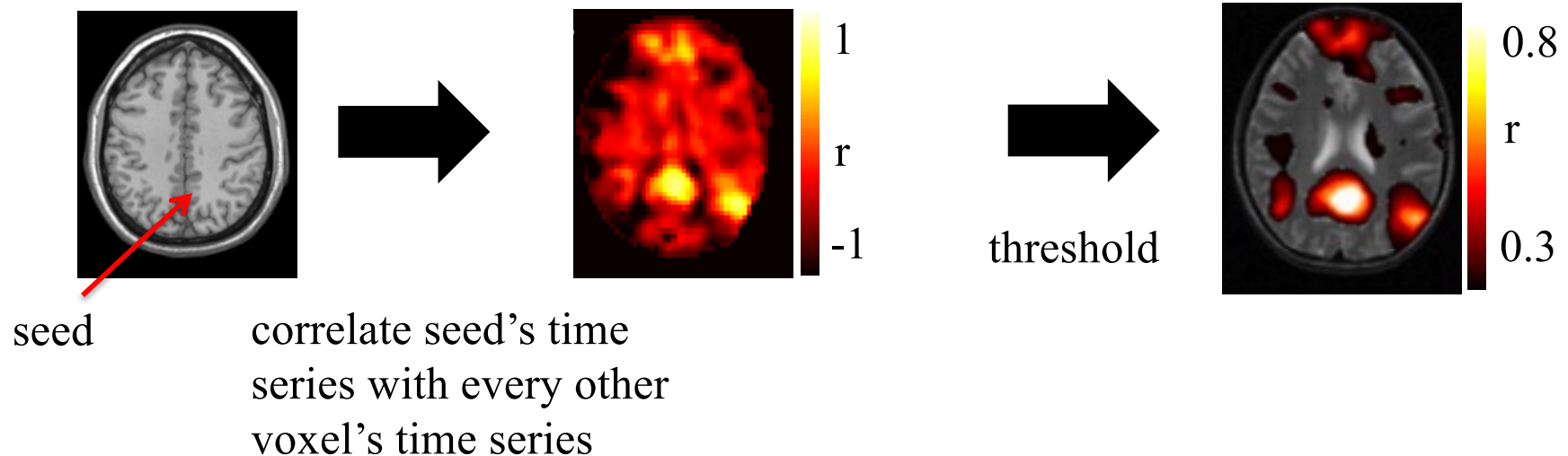
example questions:
- Are there any areas whose correlation with my seed ROI is significantly different
  in *condition A* v. *condition B*?
- Any areas whose FC with my seed ROI is proportional to [behavioral measure /
  outcome measure, etc.]

Seed-based correlation: examples

PCC seed

MT seed

MC seed

V1 seed

Fox et al. 2009

B Correlation patterns for dorsal V2 seeds in resting eyes shut data

Ipsilateral

Contralateral

S2   RH

S2   LH

V3AB
V2d V3d
V1d
hV4
V2v VO1
V1v VO2

V3AB
V2d V3d
V1d
V3 hV4
V2v VO1
VO2

Correlation (r)

0.2   > 0.7

Arcaro et al., 2015

Seed-based correlation
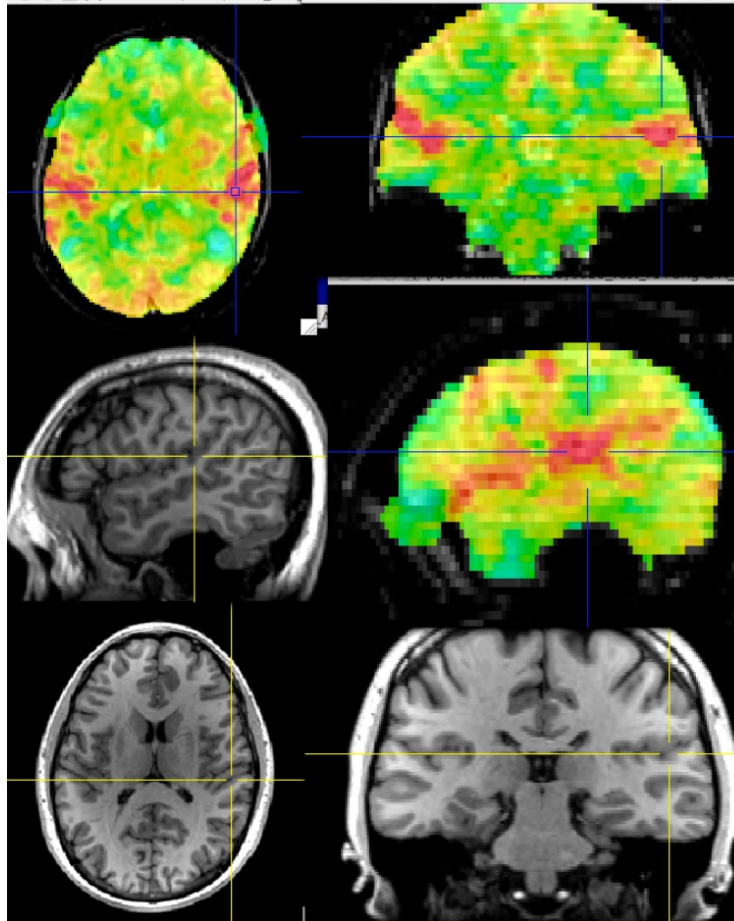
Looking at correlation maps can help to reveal artifacts
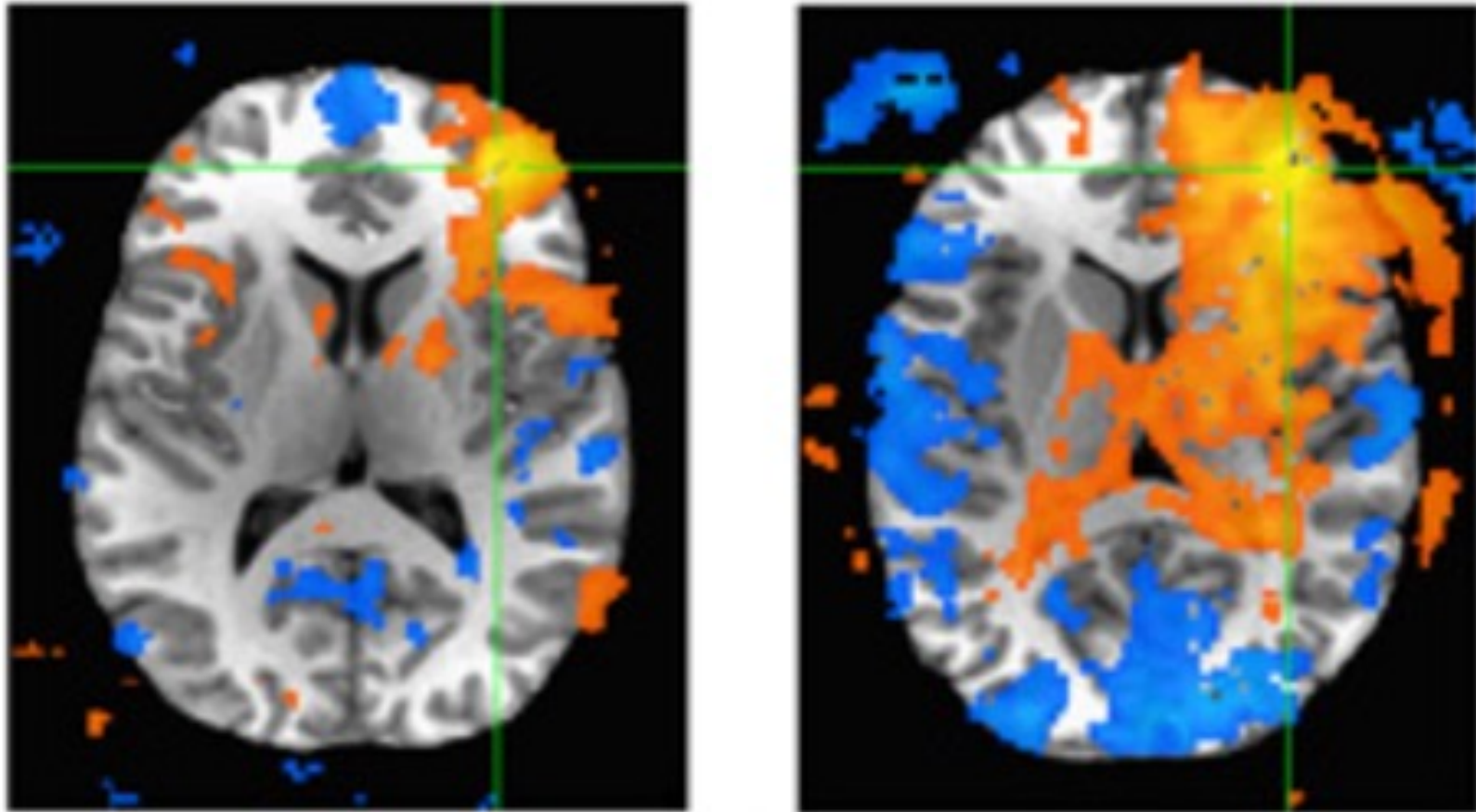
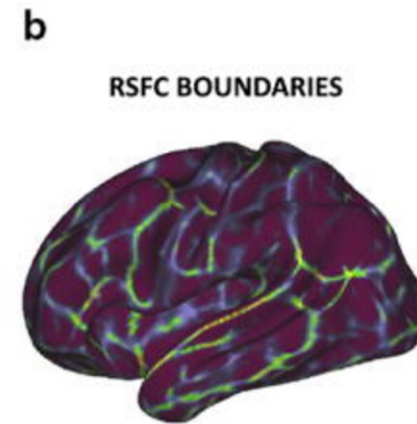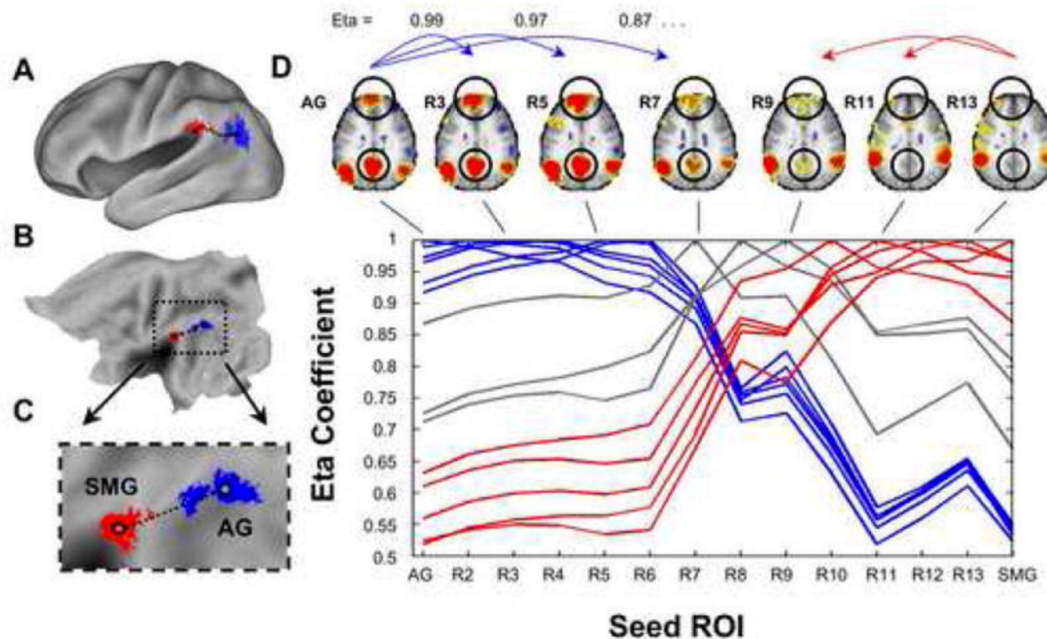*H. J. Jo et al., 2010*

Seed location?

- Placement/size of seed ROI?
  - atlas, published coordinate, structural image, activation map (single-sub, group-level)
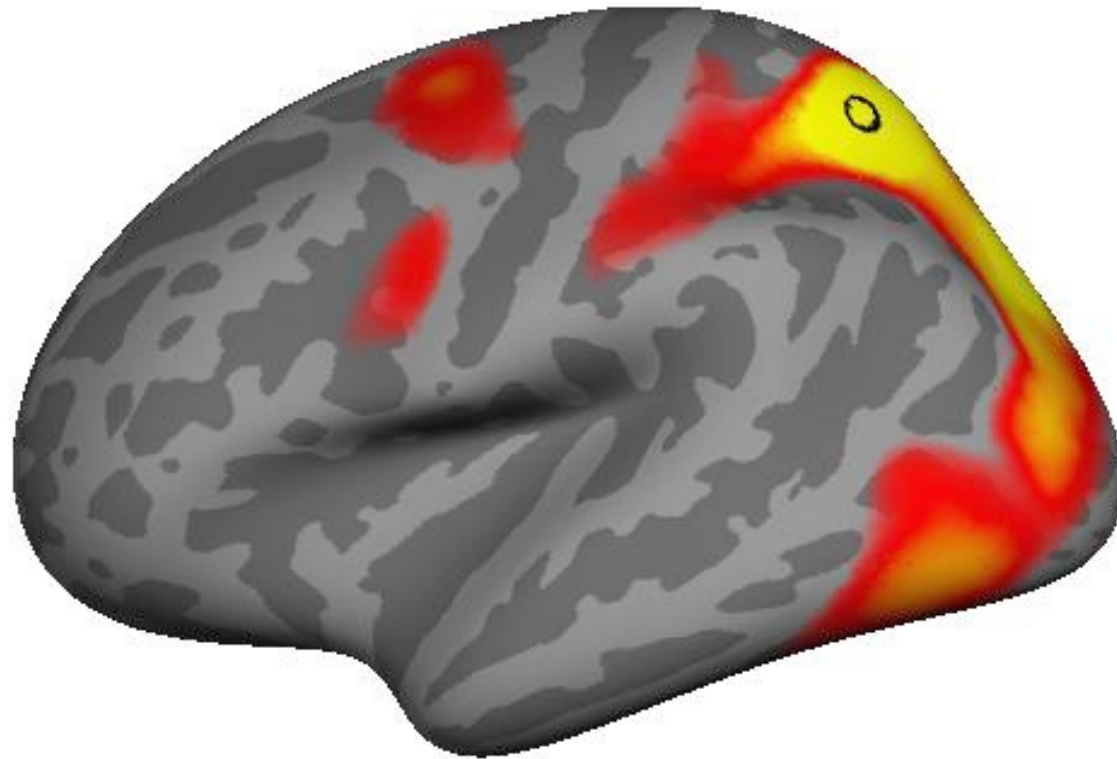

Klein et al. 2012
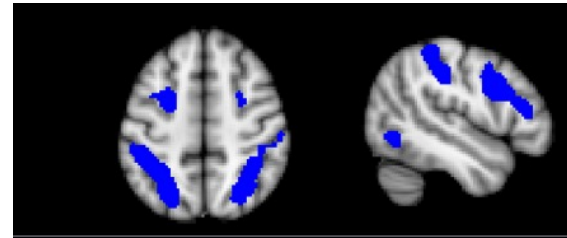
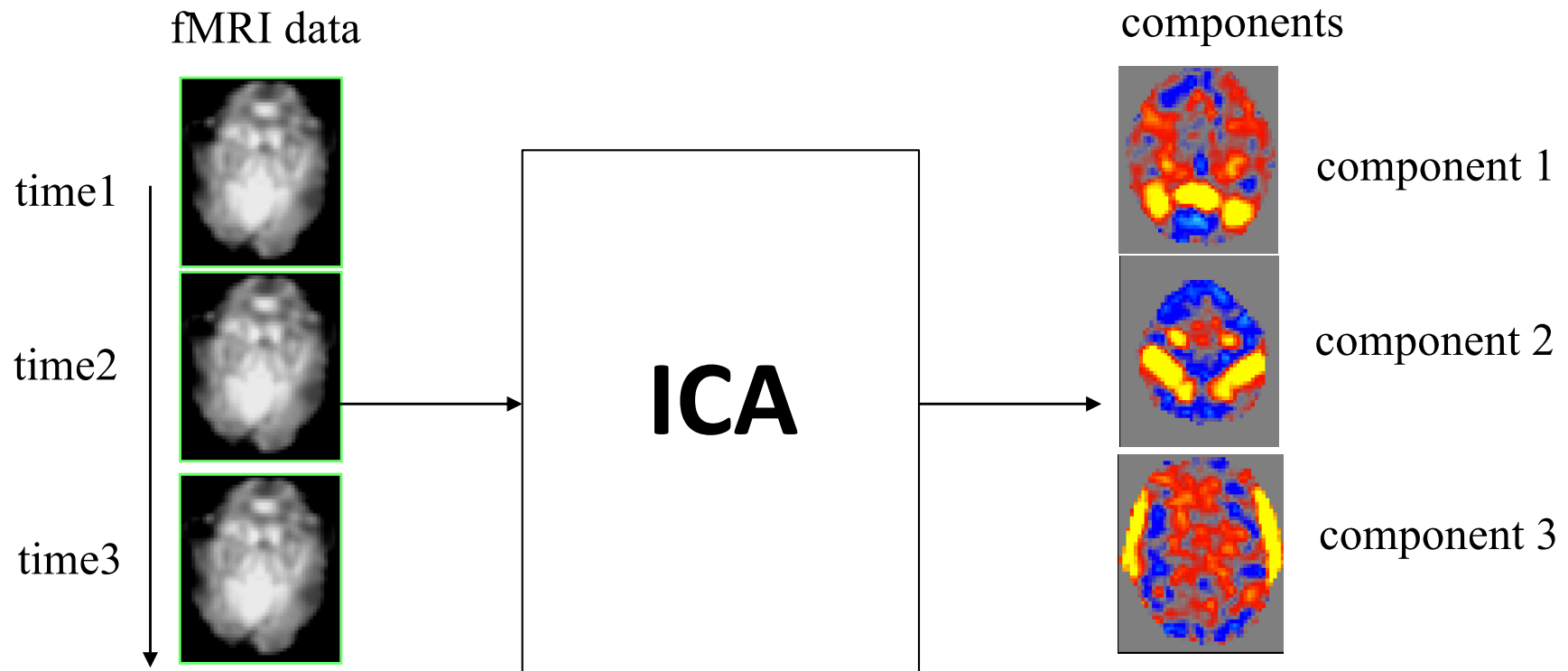*Stanford "FIND" atlas; Shirer et al. 2011*

Cohen et al. 2008

Seed-based correlation

Buckner et al. 2013

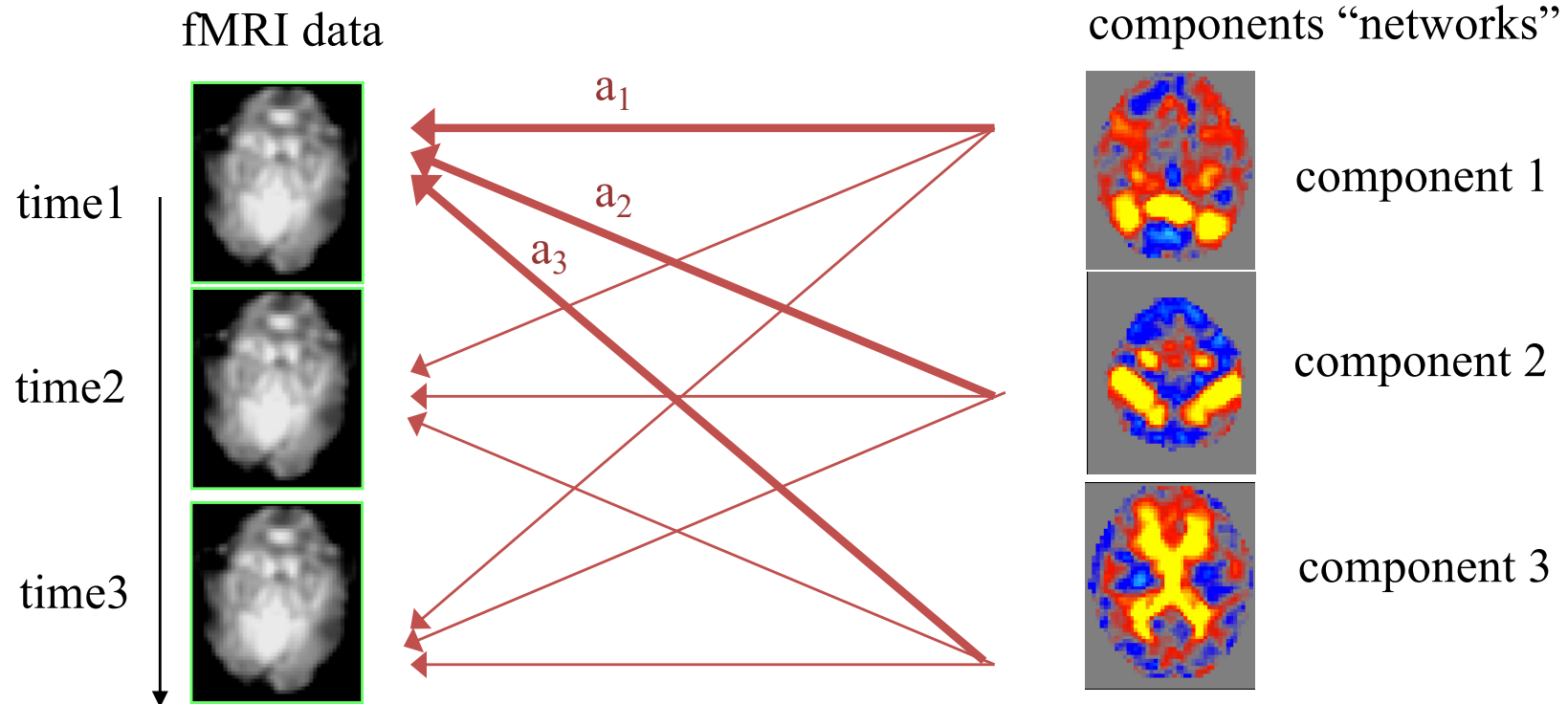# Independent Component Analysis (ICA)

fMRI data

time1

time2

time3

ICA

components

component 1

component 2

component 3

- Multivariate; many "networks" (components) at once
- Data-driven; seedless :); but need to specify some parameters
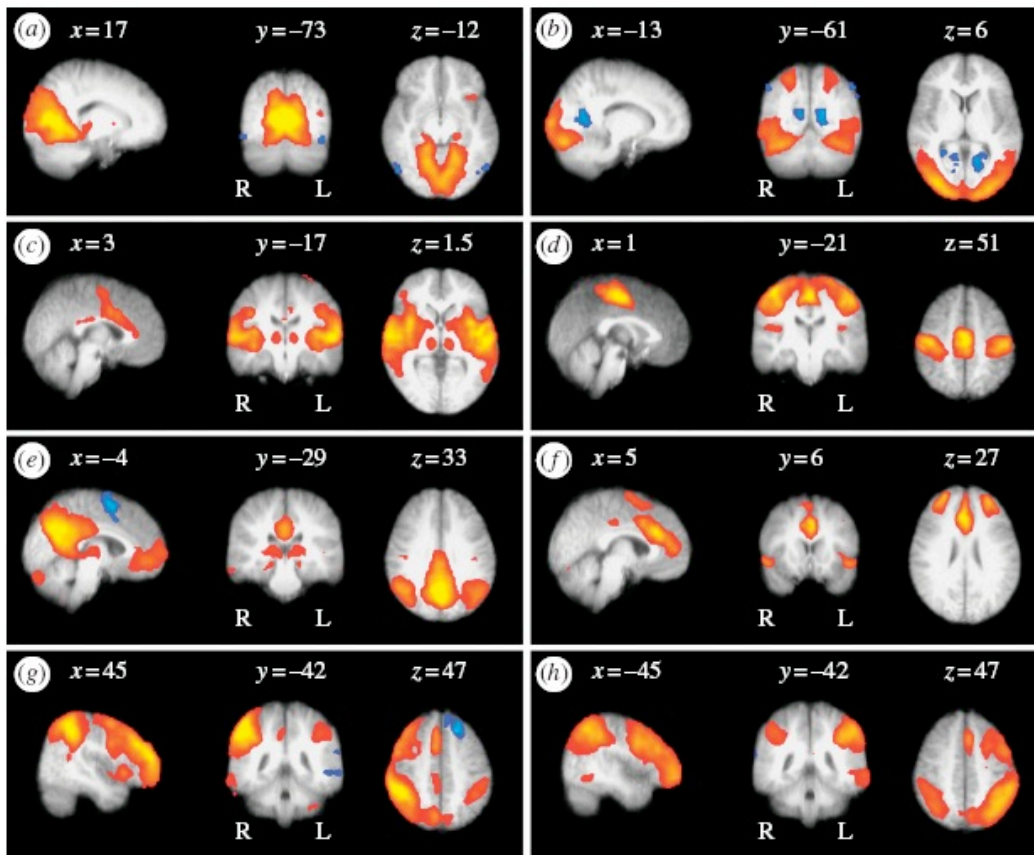- Can be used for network analysis and noise reduction
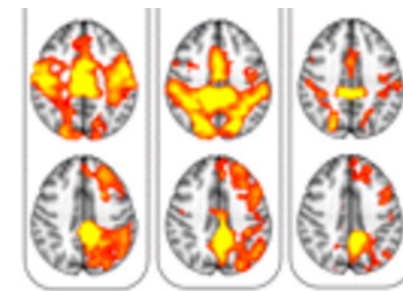
Independent Component Analysis (ICA)

fMRI data

components "networks"

time1
time2
time3

component 1
component 2
component 3
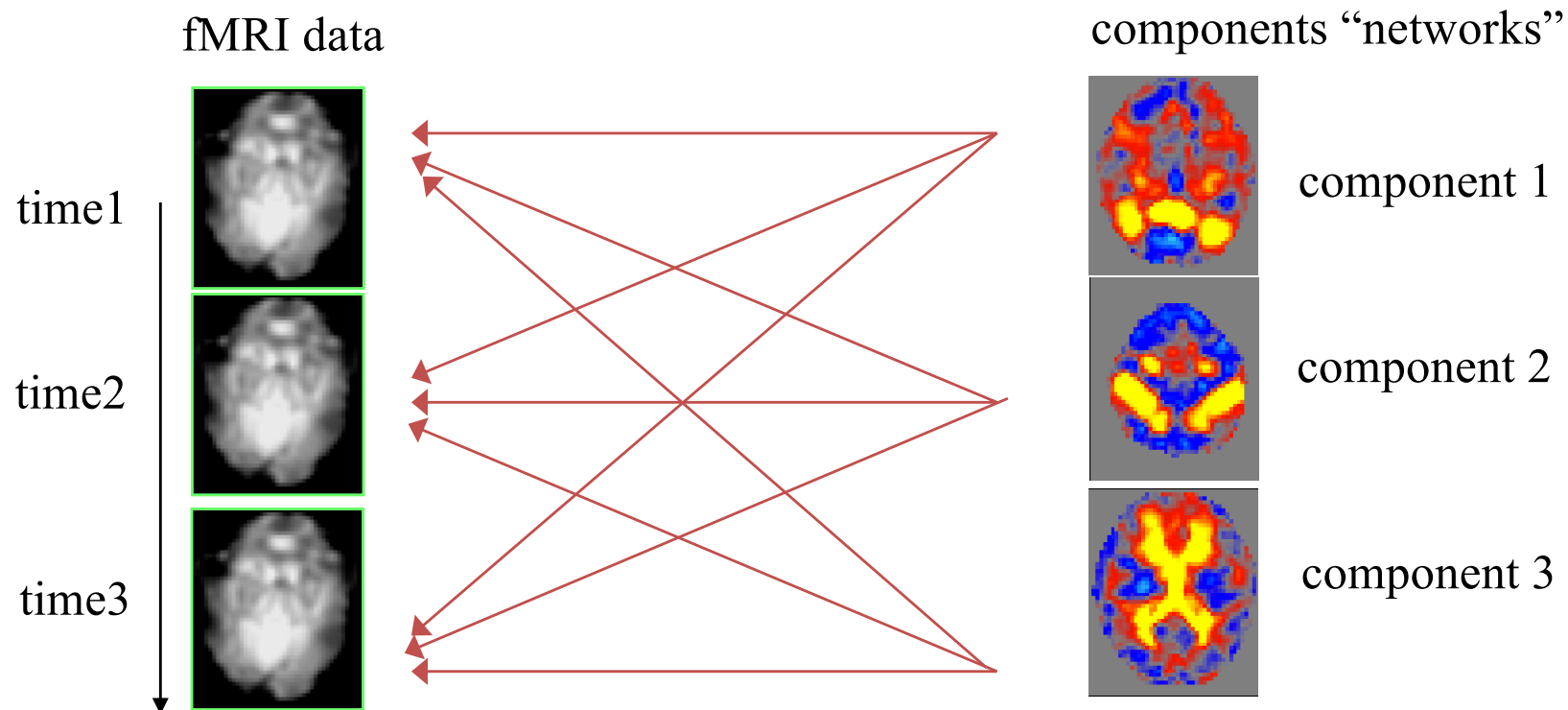
Independent Component Analysis (ICA)

"Networks" from ICA
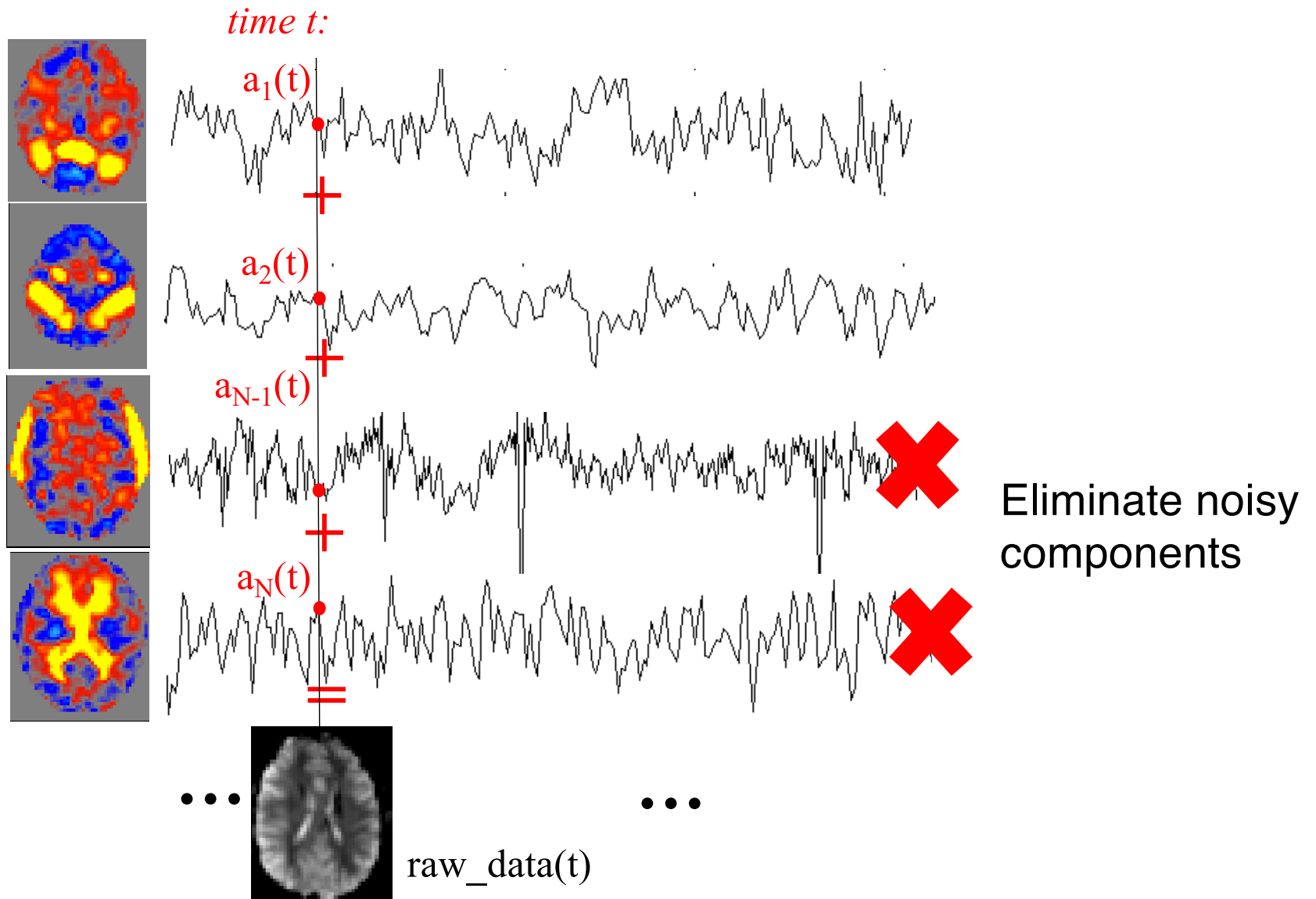

7   10   15 components

Leech et al., 2012

McKeown et al. 1998
<- Damoiseaux et al. 2006

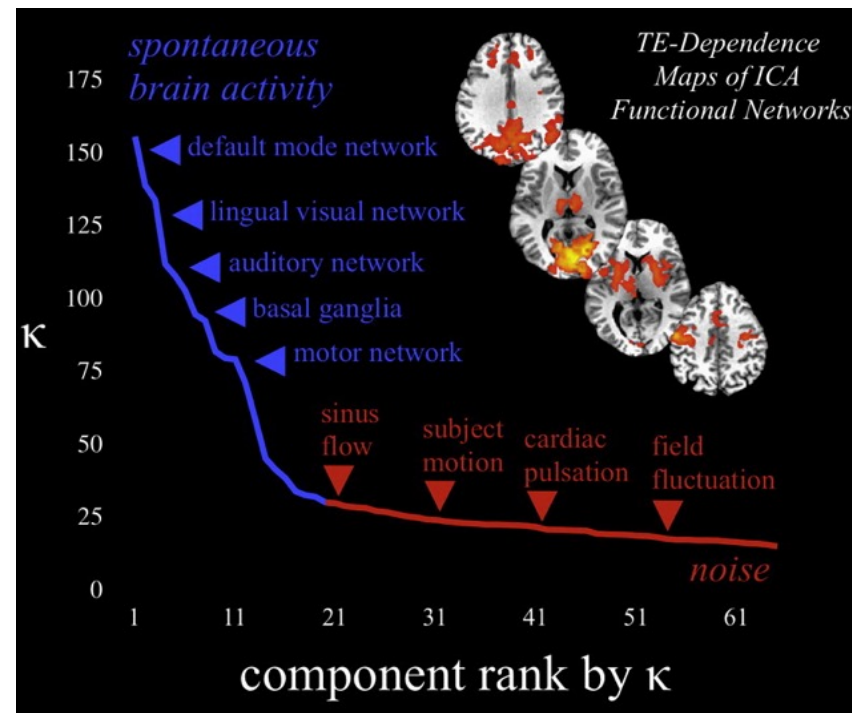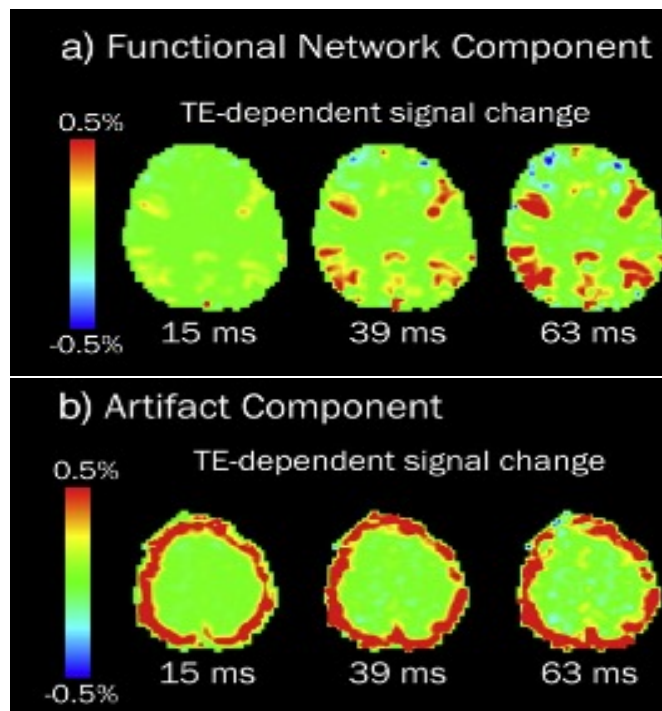-> see also: **dual regression** (Filippini et al. 2009)

Independent Components

time t:

$a_1(t)$

$+$

$a_2(t)$

$+$

$a_{N-1}(t)$ ✖

$+$

$a_N(t)$ ✖

Eliminate noisy components

$=$

··· raw_data(t) ···

Identifying noise components?

- FIX: "FMRIB's ICA-based Xnoiseifier"

http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIX

- Multi-echo ICA

*Kundu et al, 2012, 2013*

ICA: considerations

- How many components to ask for?
  - Heuristics, but no "best" way
  - Similar networks may split when increasing # components
- Interpretation more complicated than seed-based
  - Algorithm, non-biological criterion: spatial independence
- Must select noise v. neural components
  - There are methods for automated selection (multi-echo ICA; "FIX")
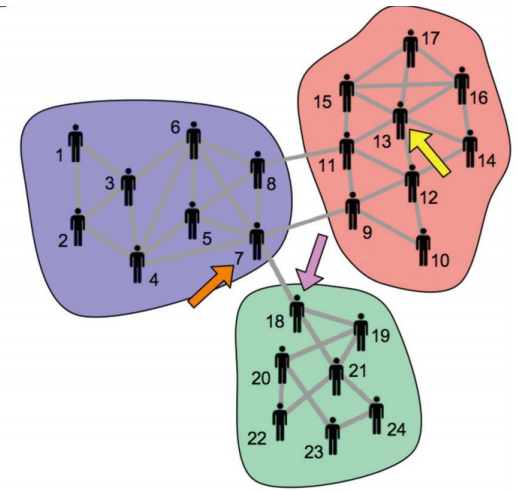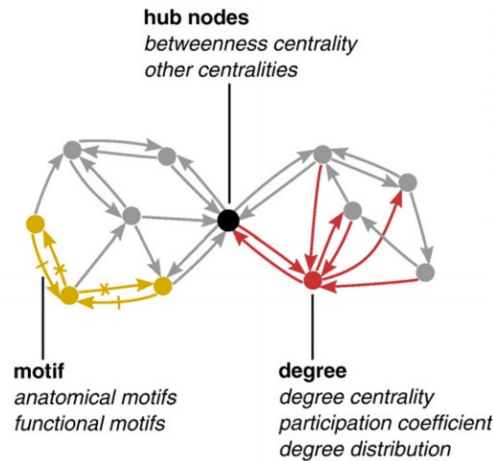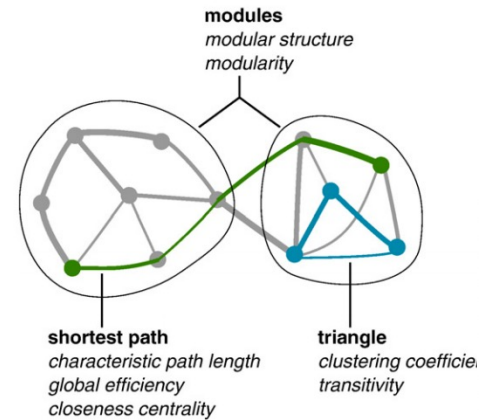 - Not a clean separation
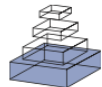
Advances and pitfalls in the analysis and interpretation of resting-state FMRI data

David M. Cole[1], Stephen M. Smith[2] and Christian F. Beckmann[1,2]*

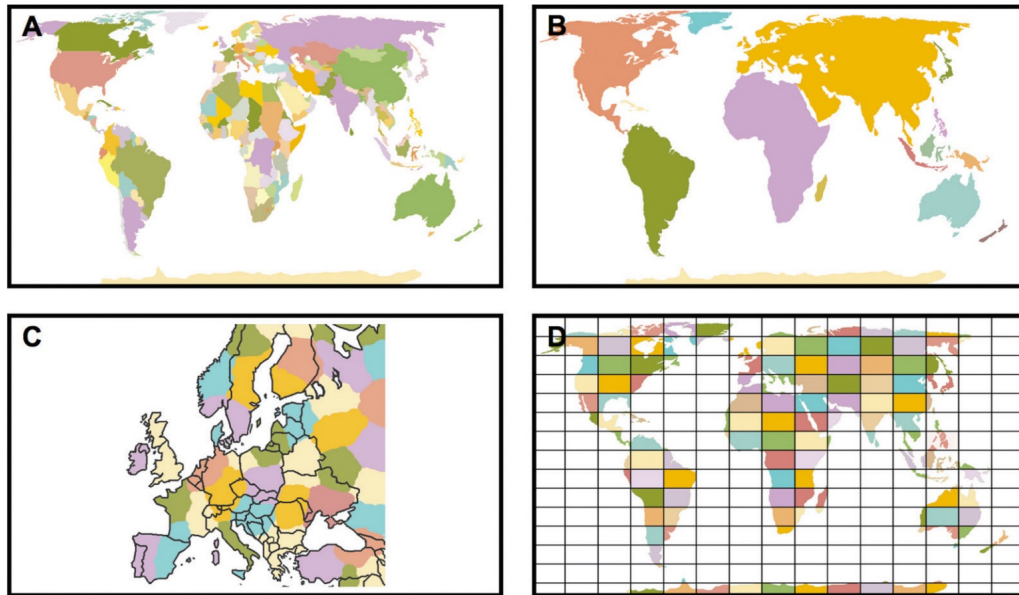# Complex network analysis
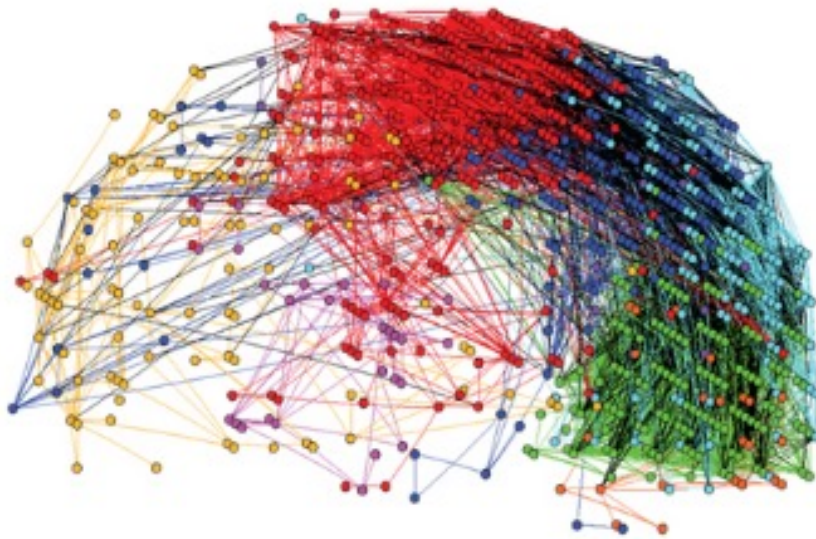
Meunier et al. 2011

Wig et al. 2011
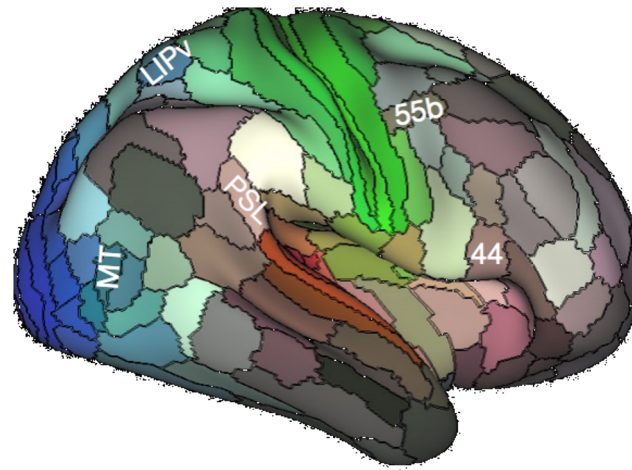
Reviews:
Rubinov & Sporns, 2010
Bullmore & Sporns, 2009

Node definition (*parcellation*)

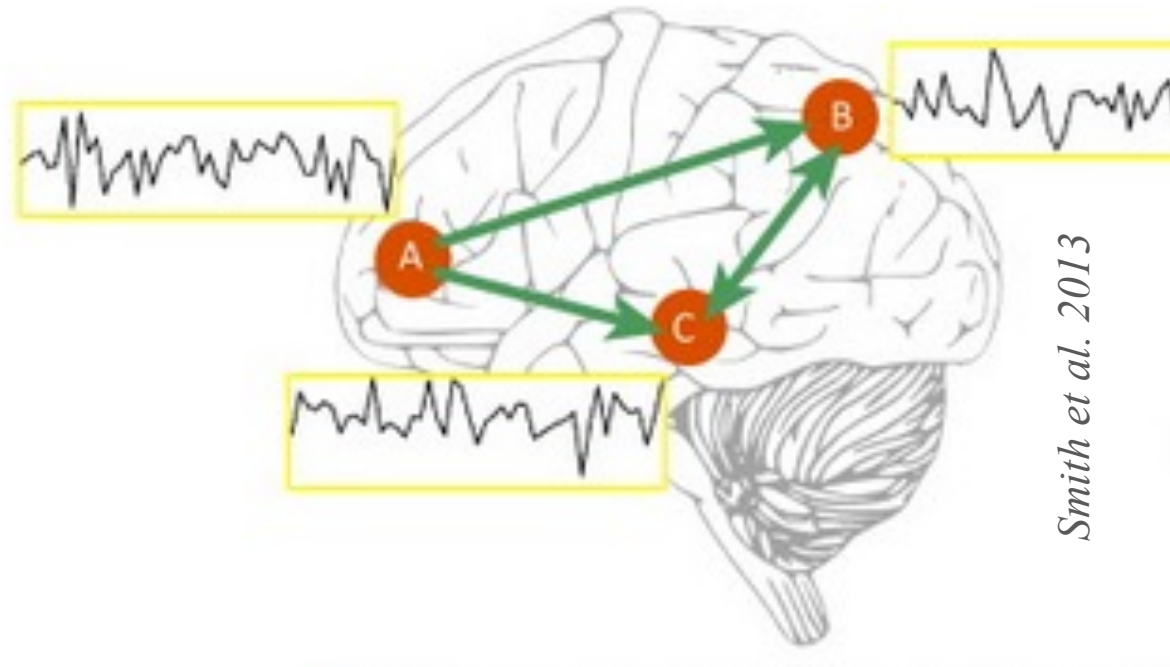*Wig et al. 2011*

Craddock et al. 2012

200 ROIs

1000 ROIs

Glasser et al. 2016

LIPv
55b
PSL
MT
44

Outline

- Background & motivation
- Analyzing resting-state data
- **Issues, caveats, and interpretation**
- Directions

Functional connectivity is a powerful but ambiguous mapping tool
(Buckner et al. 2013 Nat. Neuro)

Smith et al. 2013

- Difficult to isolate process of interest
- Noisy; sensitive to modeling and pre-processing decisions
- Relationship with structural connectivity & electrophysiology not straightforward

Physiological noise

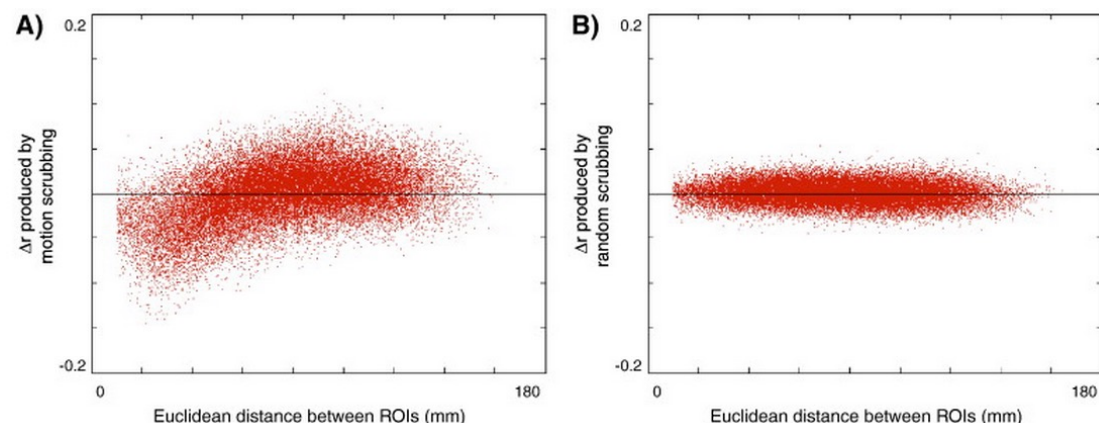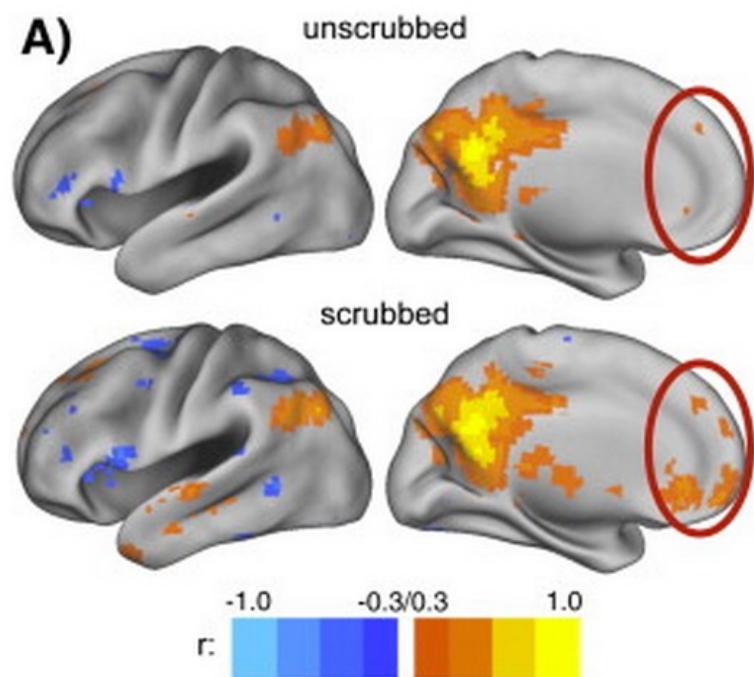- Any non-neural fluctuations shared in common across regions will create the appearance of "functional connectivity"
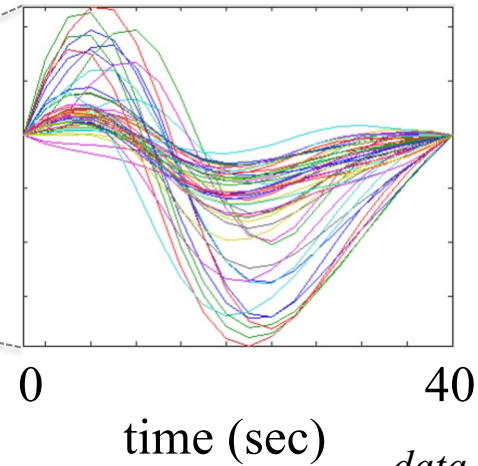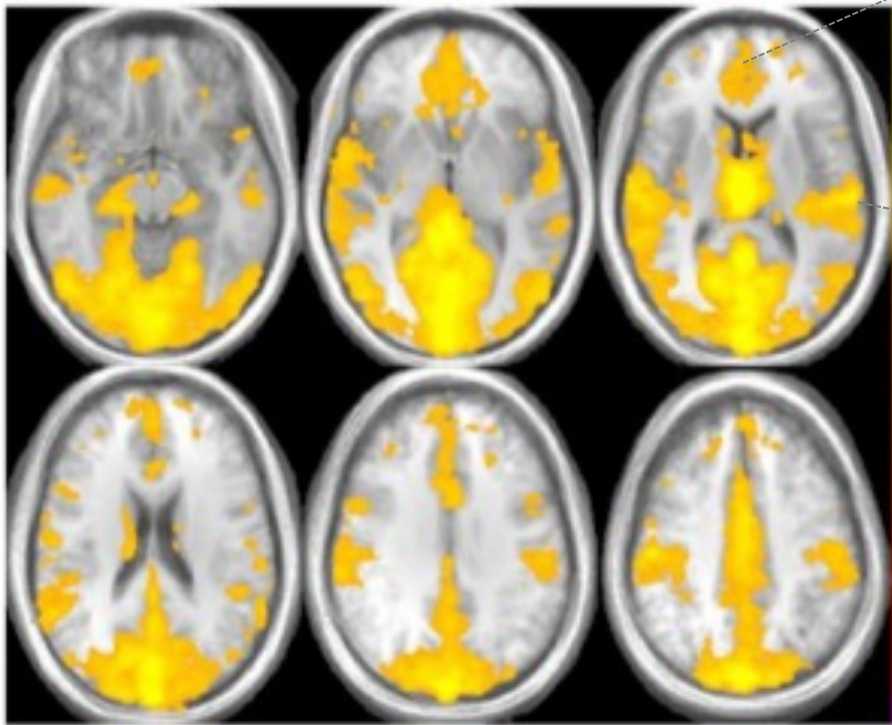
data from Chang et al. 2009

Birn et al. 2006

Head motion
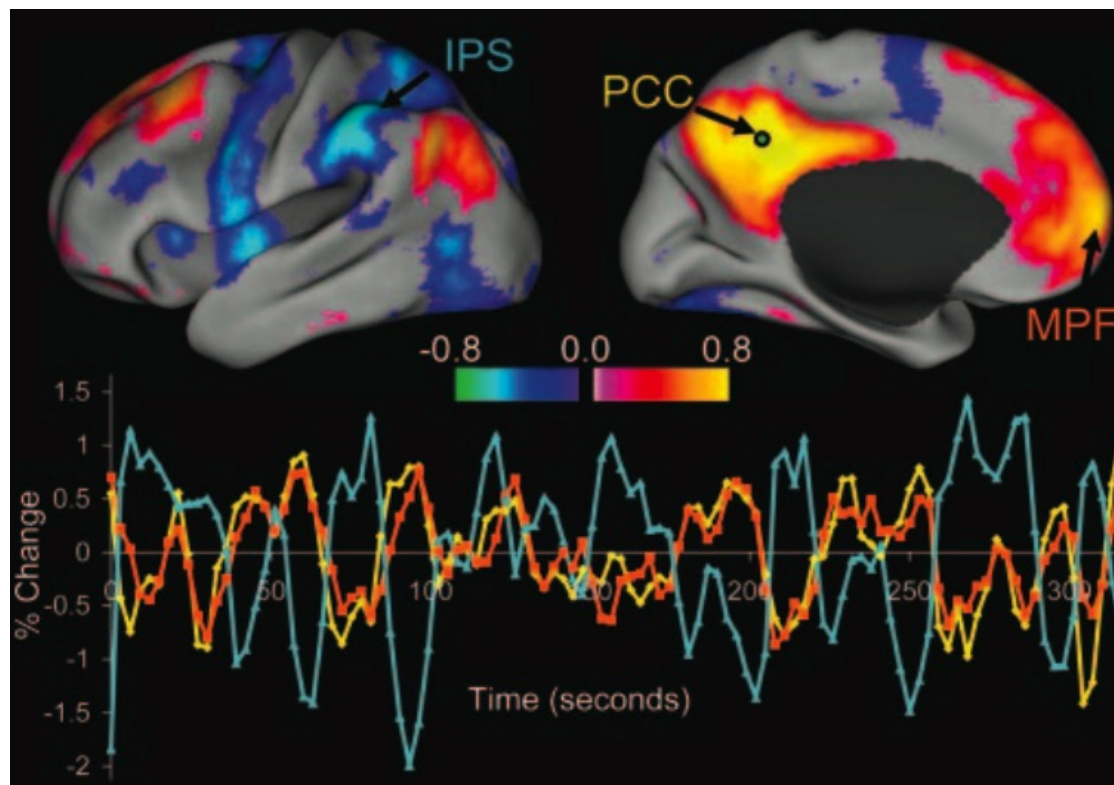

Power et al. 2012

- Systematic differences in head motion across age groups caused spurious functional connectivity effects

What is noise, what is signal?

- no task/stimulus timing to help distinguish signal from noise

- trial averaging not possible

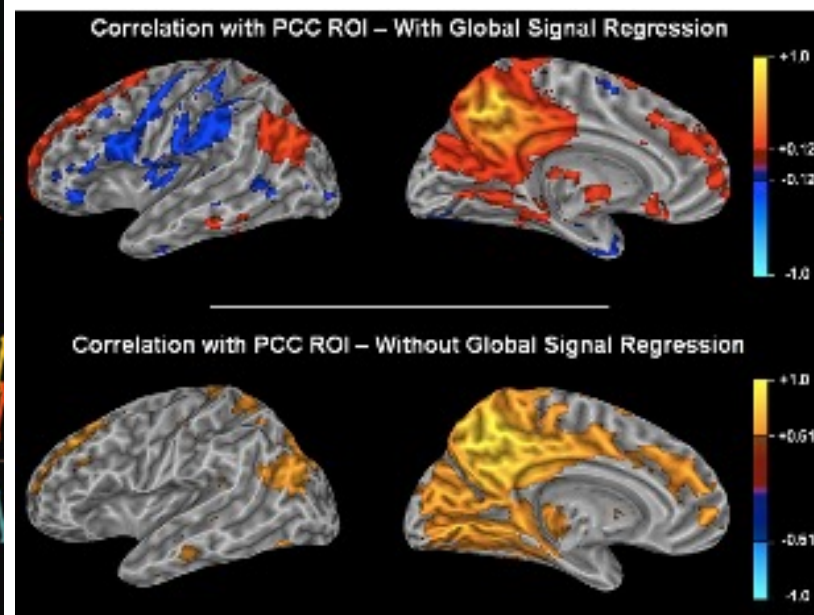- "functional connectivity" quantifies relationships between regions (each are signal + noise!)
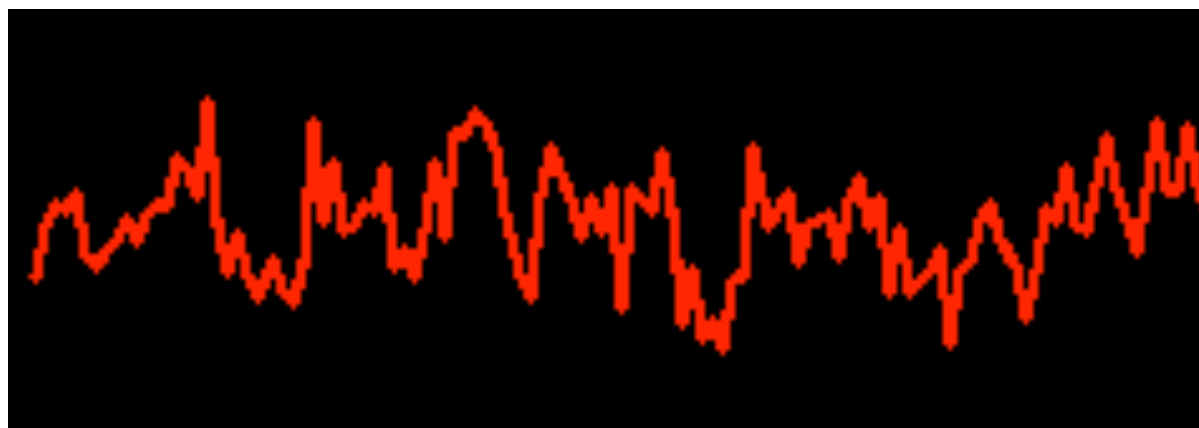
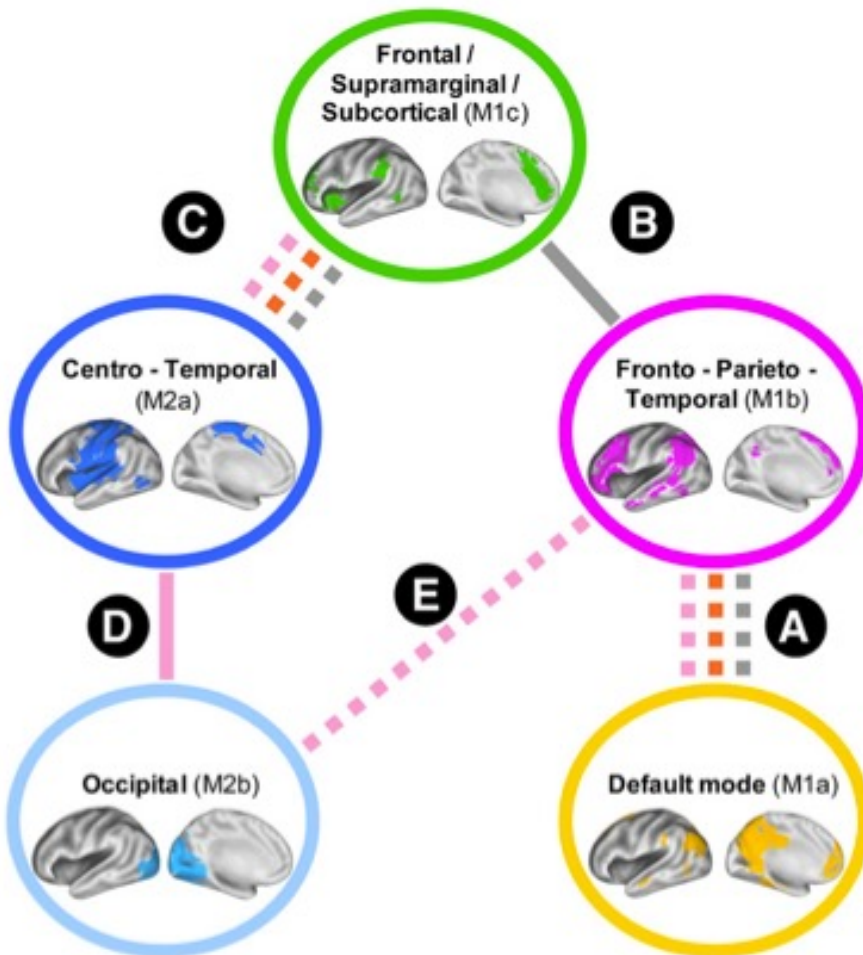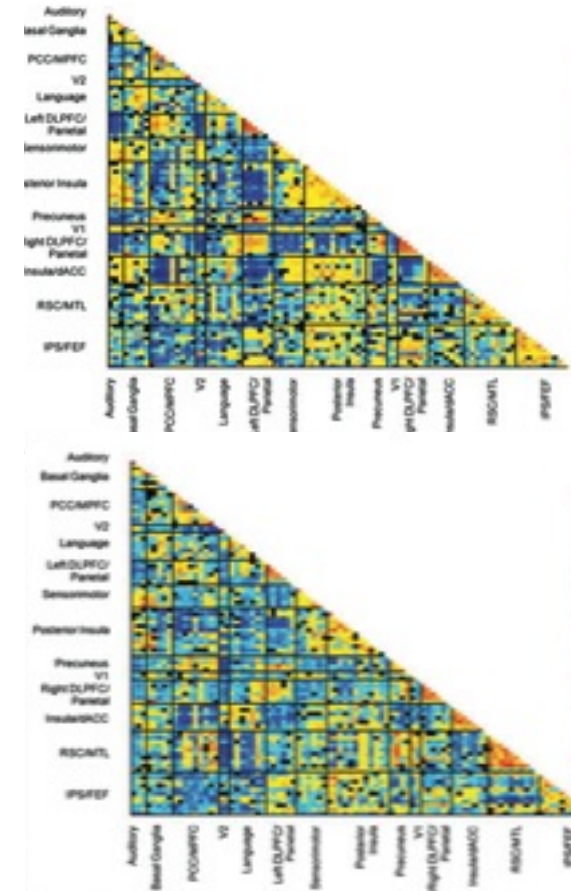# Noise-reduction strategies can affect results

Fox et al, 2005
Fransson 2005

Murphy et al, 2009

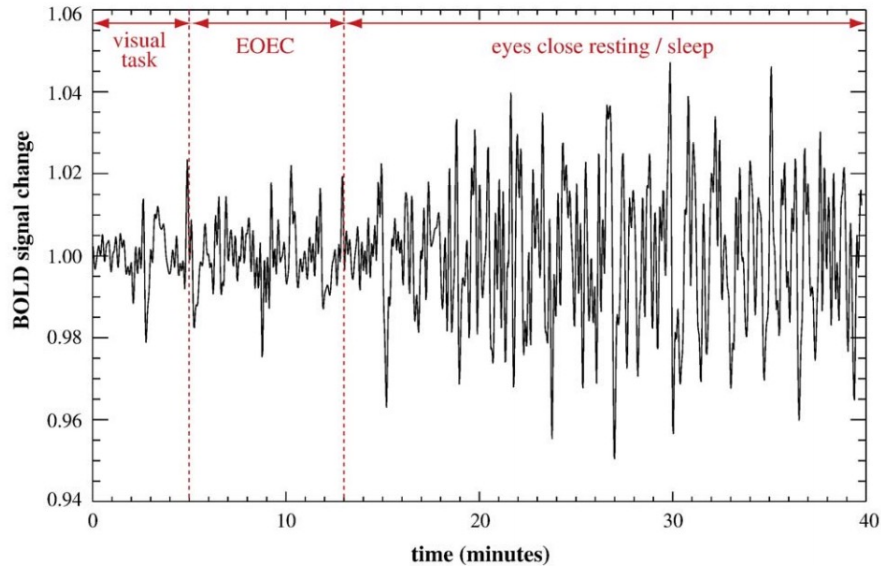- how can we tell which is correct?

Thoughts, mind-wandering

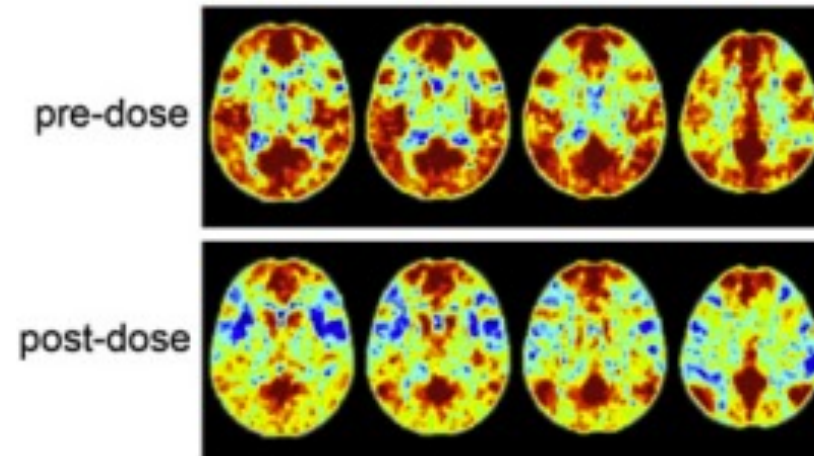Doucet et al. 2011

Shirer et al, 2011

Drowsiness

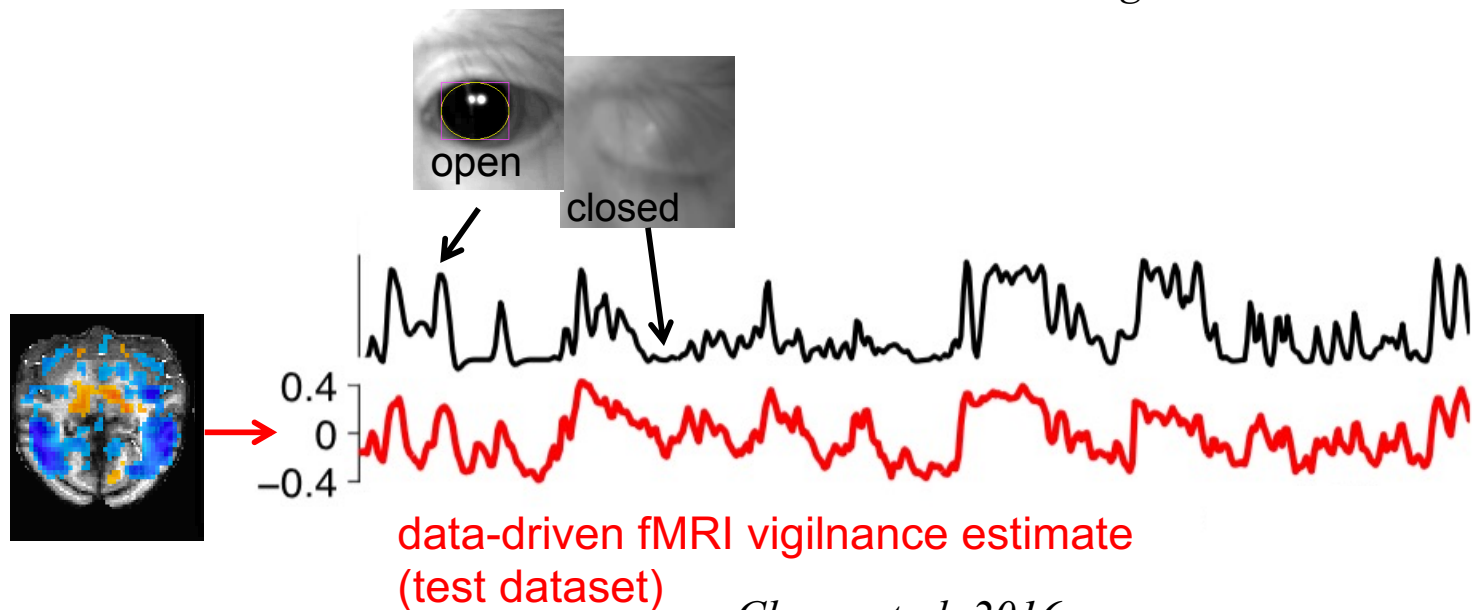*Fukunaga et al. 2006*

before v. after caffeine

Wong et al. 2010

open

closed

FNI: analysis_2/intersub_eyeCorrelMaps/frenzy_t1_avg_reg2_bet.nii.gz+orig & template_S_alignFrenzy_bet....

July 12, 2017
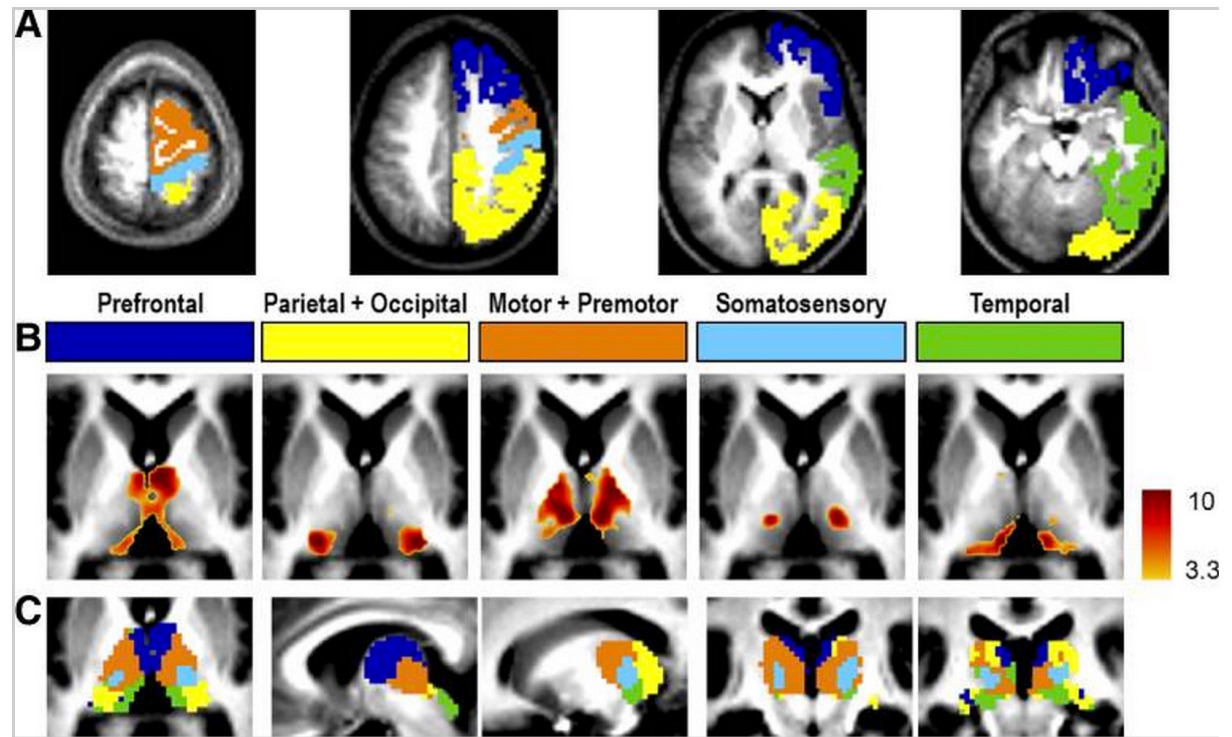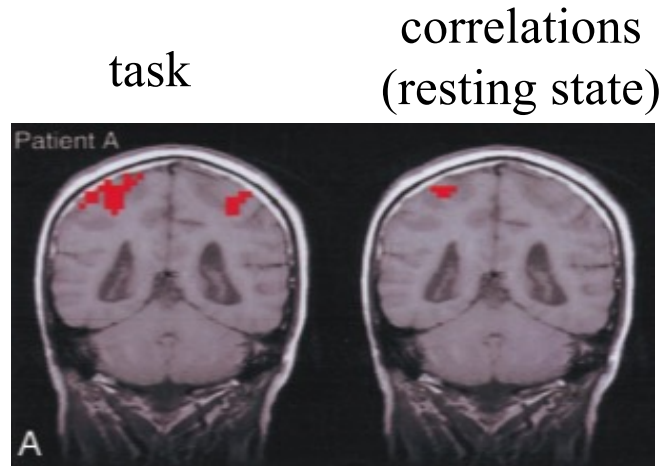
Correspondence with structural connectivity
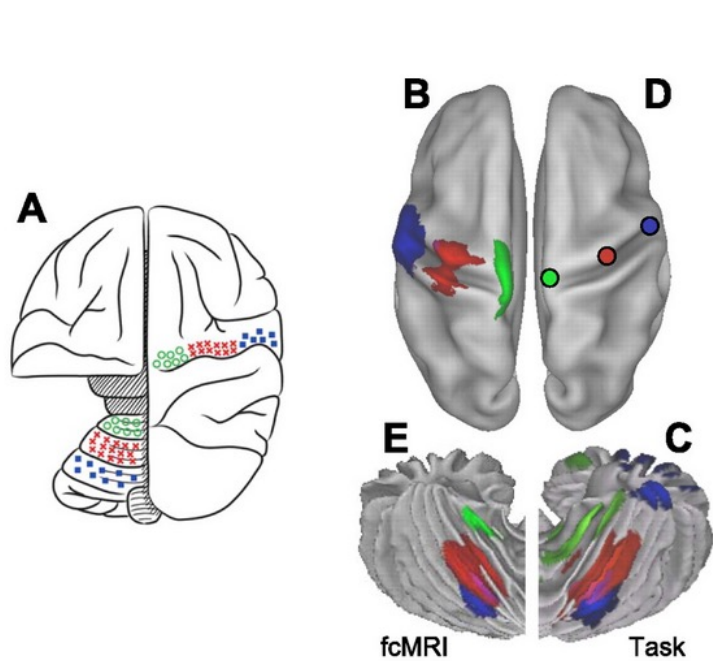
Buckner et al. 2011

Zhang et al. 2008

Correspondence with structural connectivity
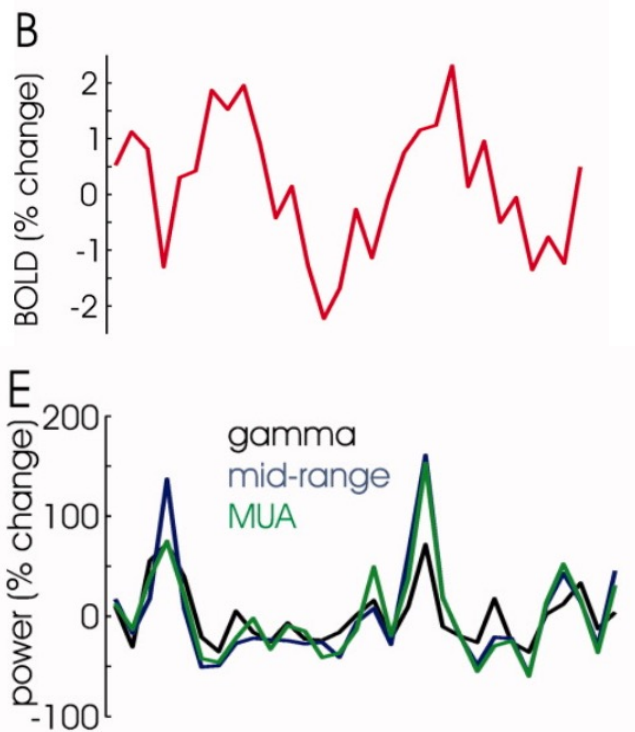
Agenesis of the Corpus Callosum

task

correlations
(resting state)

Quigley et al., 2003
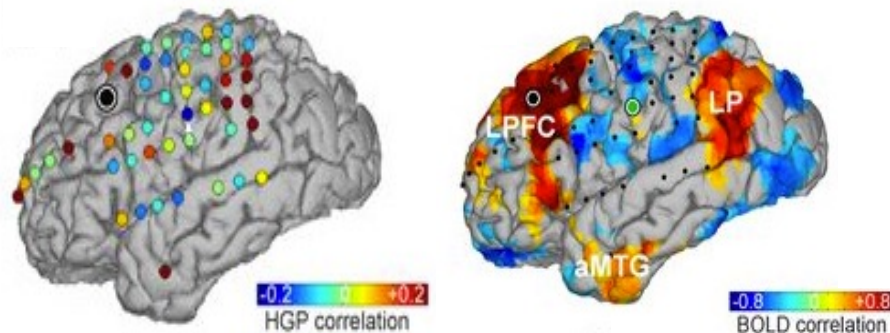
Johnston et al., 2008

via indirect
connections?
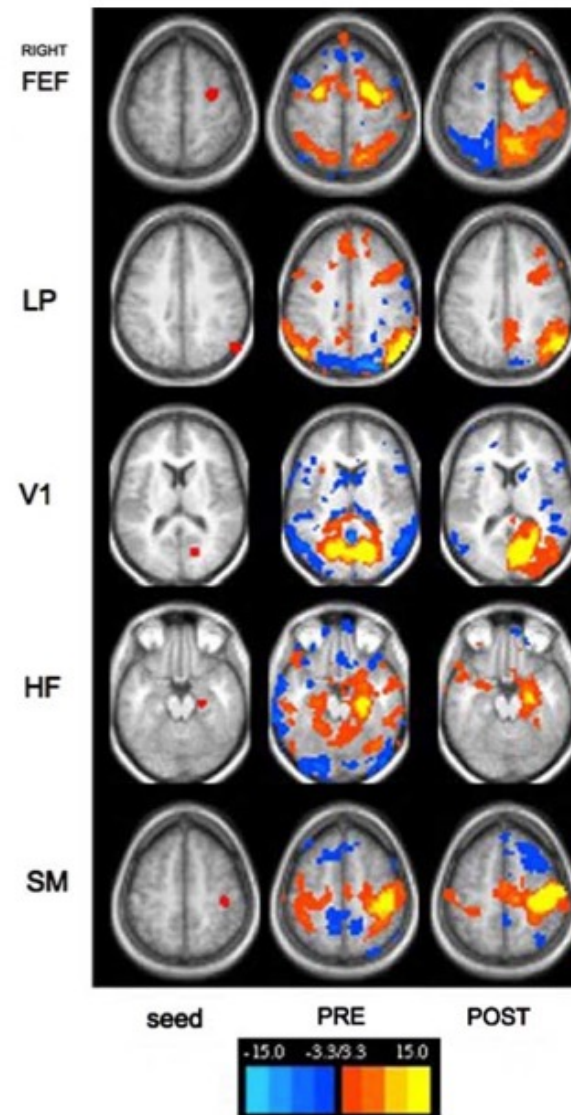
Electrophysiological correlates

Spontaneous fMRI signal

Shmuel & Leopold, 2008
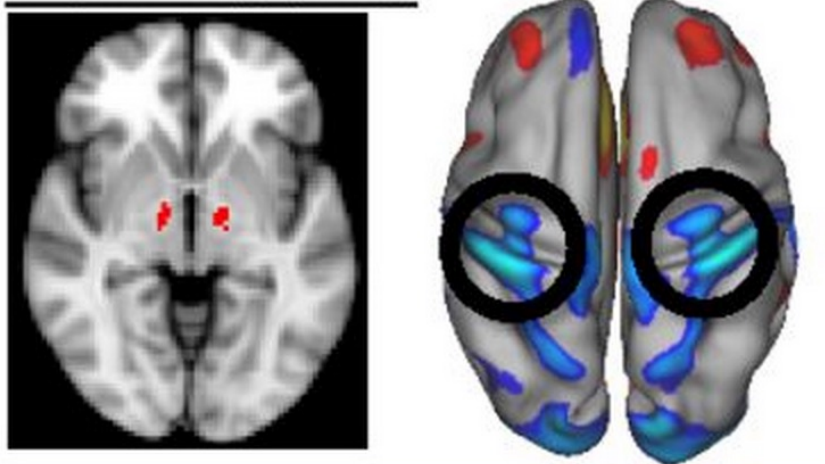

Keller et al. 2013

- slow cortical potential (e.g. He et al, 2010)
- distributed across frequency bands
  (e.g. Mantini et al. 2007)
- broadband (e.g. Liu et al. 2014)
- *review*: Scholvinck et al. 2013

Outline
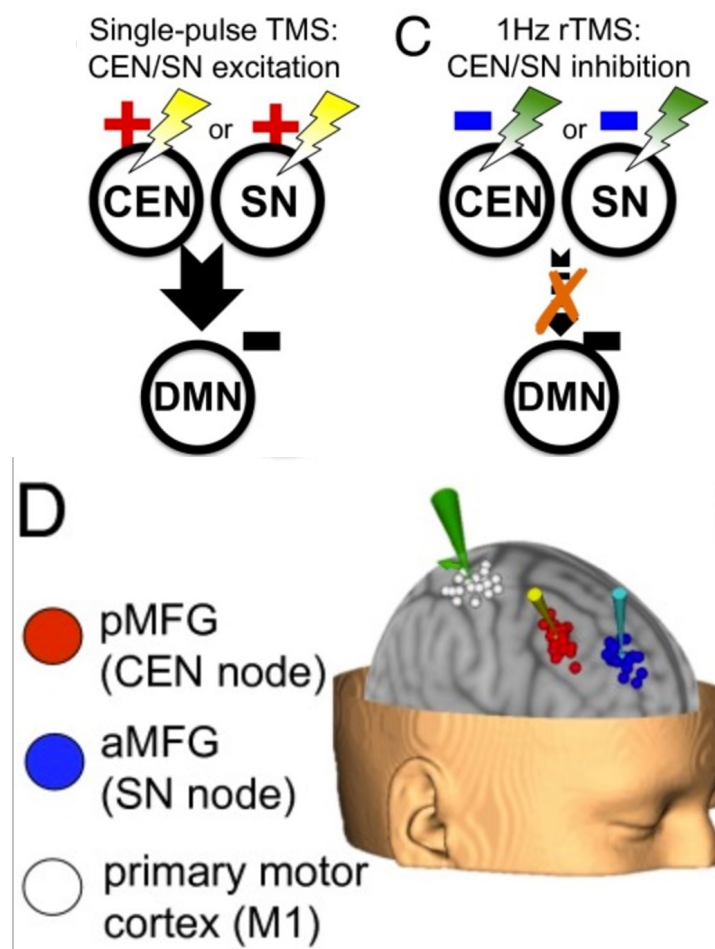
- Background & motivation
- Analyzing resting-state data
- Issues, caveats, and interpretation
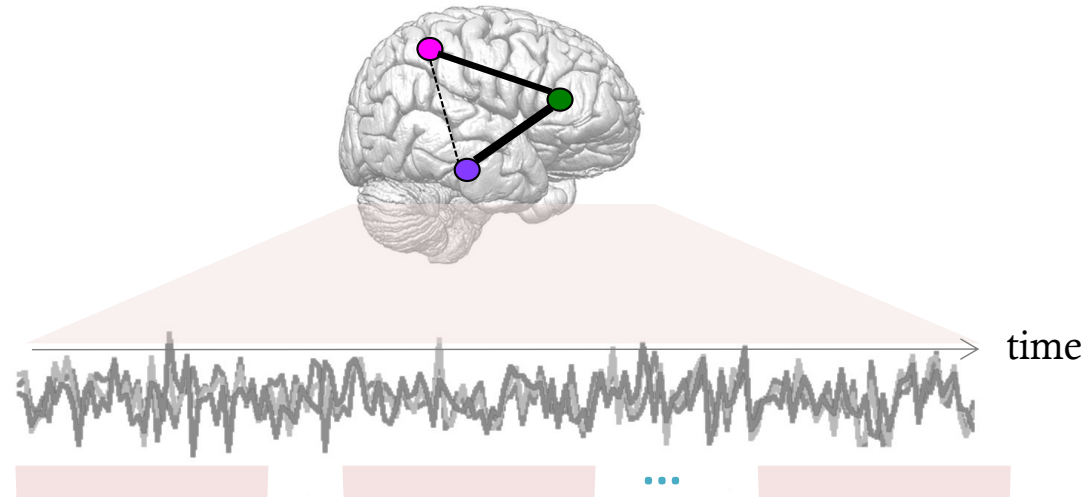- **Directions**

Resting state & brain stimulation

Fox et al. 2014

Chen et al. 2013

"Dynamic" brain connectivity

"static"

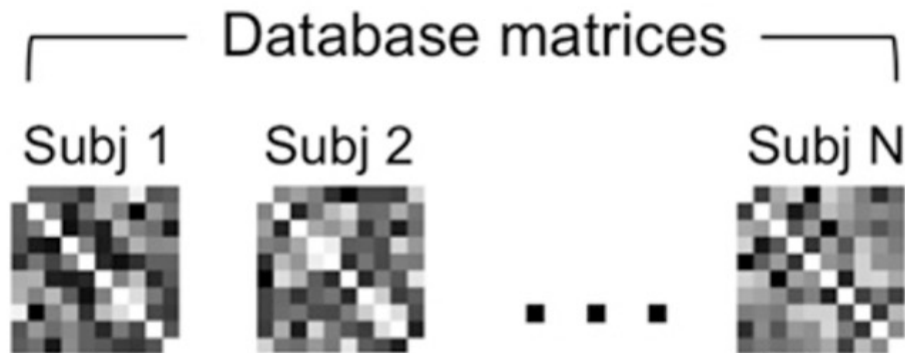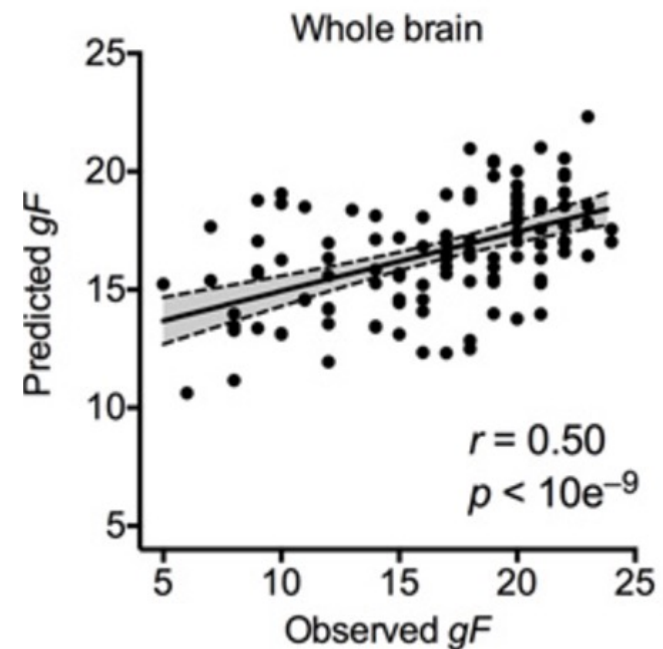
"dynamic"

time
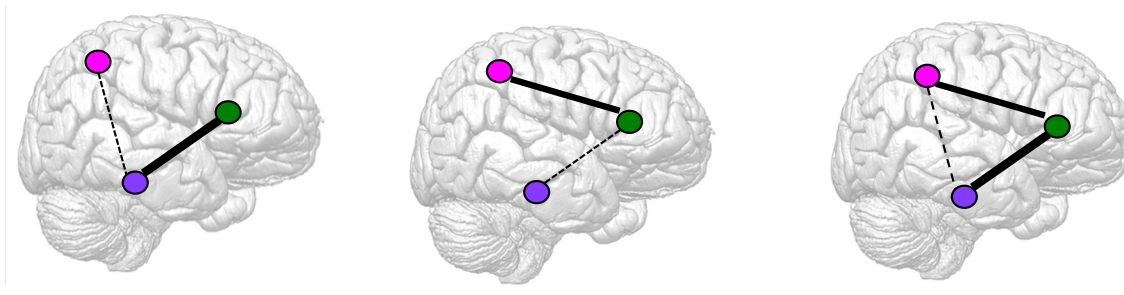
Functional connectivity & individual differences

Database matrices

Subj 1   Subj 2   ...   Subj N

Finn, Shen et al. 2015

Whole brain

$r = 0.50$
$p < 10e^{-9}$

Predicted *gF*

Observed *gF*

Data sharing & big data

The WU-Minn Human Connectome Project: An overview

David C. Van Essen [a,*], Stephen M. Smith [b], Deanna M. Barch [c], Timothy E.J. Behrens [b], Essa Yacoub [d], Kamil Ugurbil [d], for the WU-Minn HCP Consortium

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[c] Psychology Department, Washington University, St. Louis, MO 63105, USA
[d] Center for Magnetic Resonance Imaging, University of Minnesota, Minneapolis, MN 55455, USA
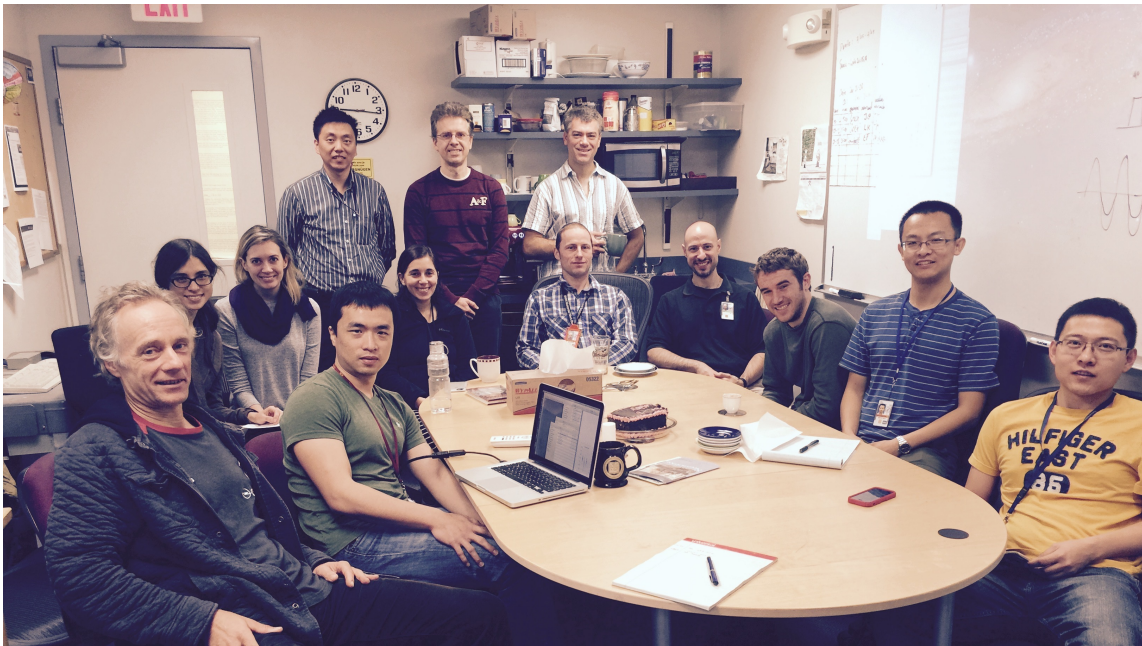
Summary

- Resting-state fMRI data exhibit spatio-temporal organization
- widely studied for clinical applications and basic neuroscience

- Understand analysis methods/tradeoffs
  - and stay close to the data

- Noise and neural variability can affect signal and connectivity measurements
  - control for as much as possible

Thanks!

AMRI Lab @ NIH

Jen Evans