# “Resting-state” fMRI

SPM Course Zürich, 04-Feb-2015

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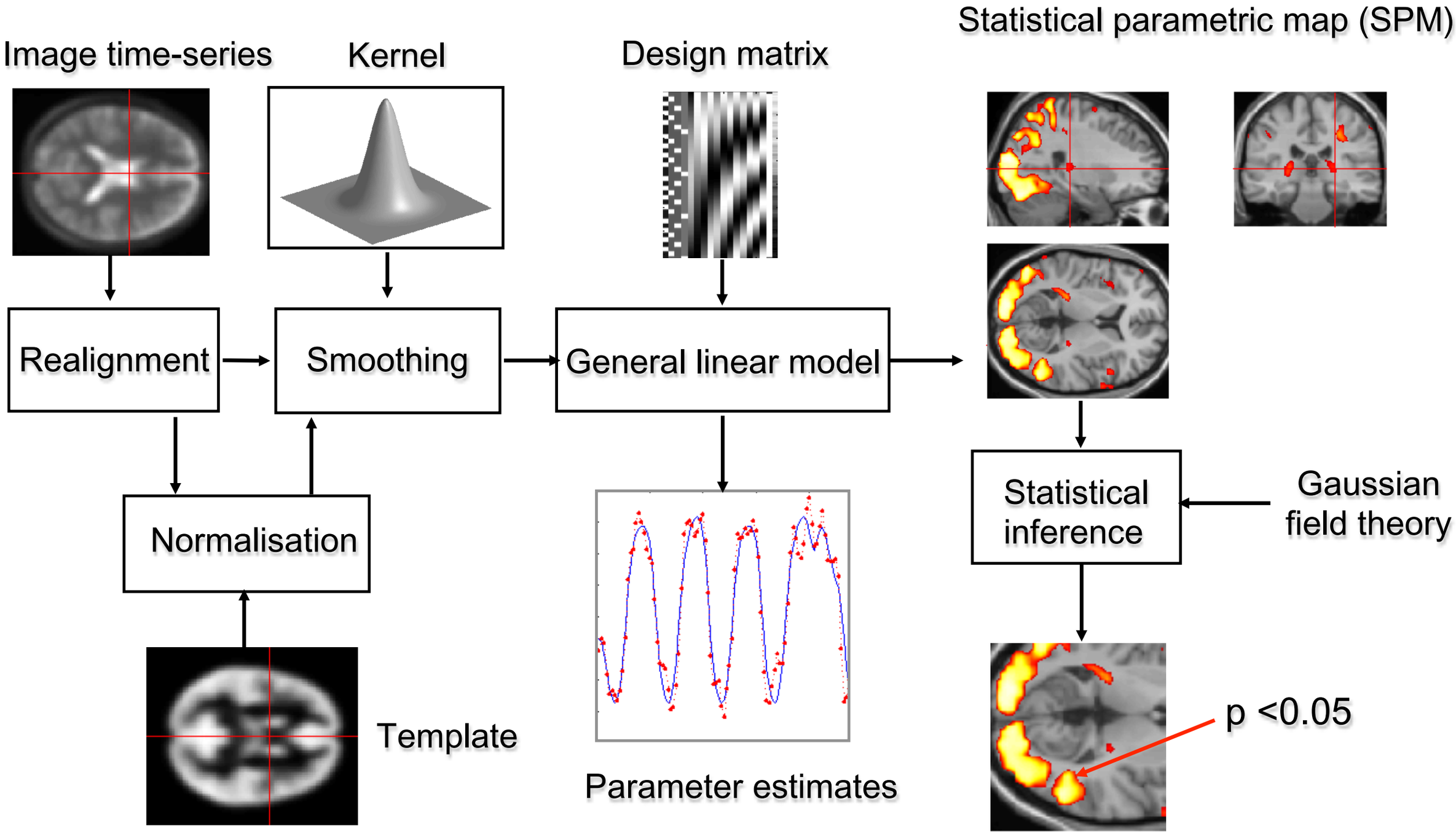
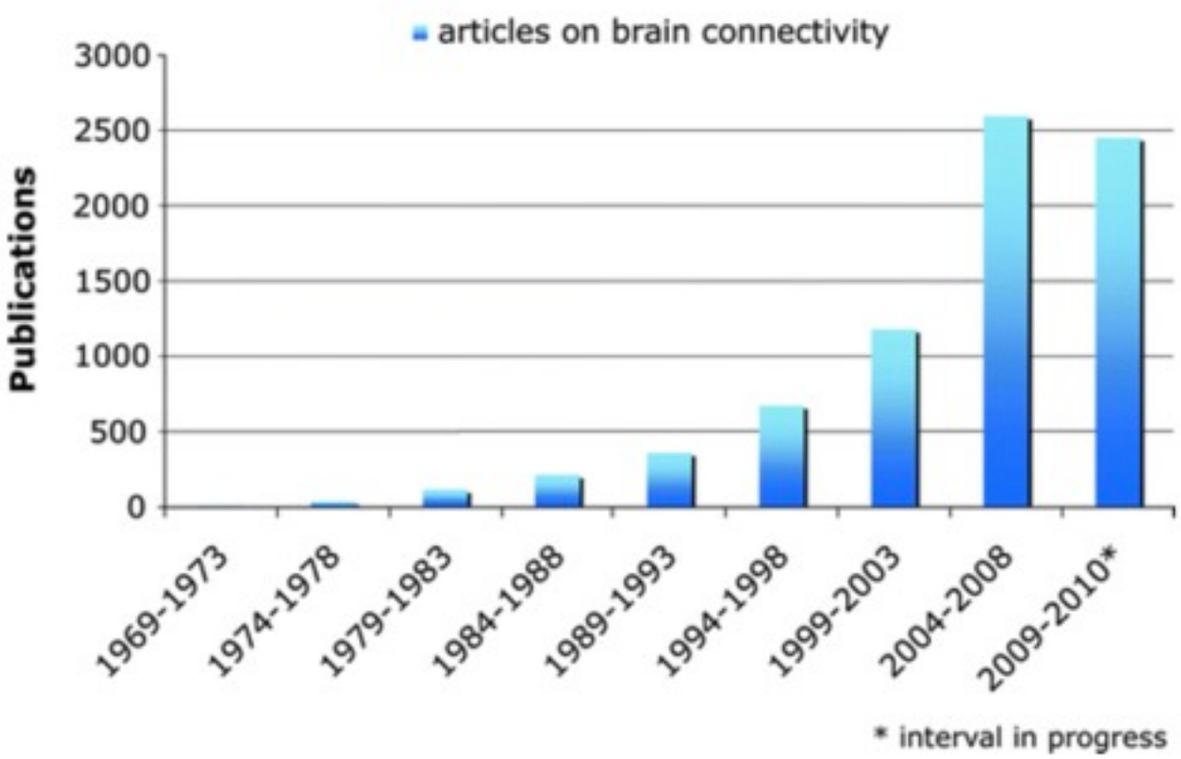
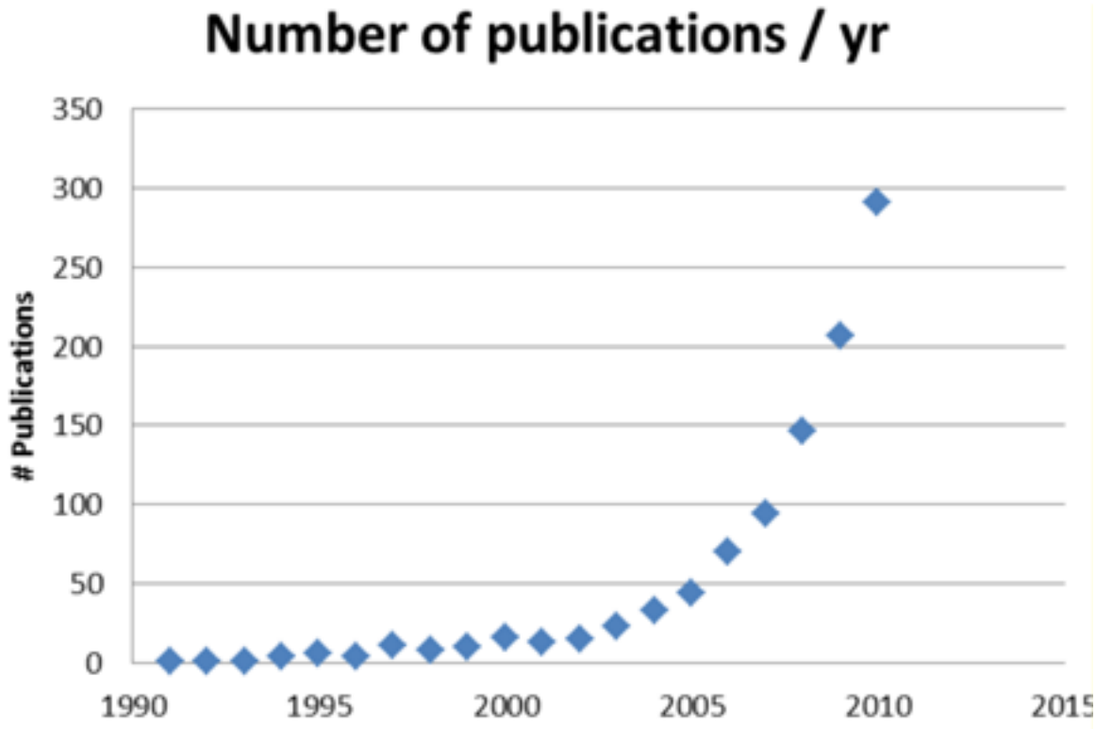
# Overview of SPM – Resting state fMRI



# ‘Exponential’ interest




Pawela & Biswal (2011) *Brain Connectivity*

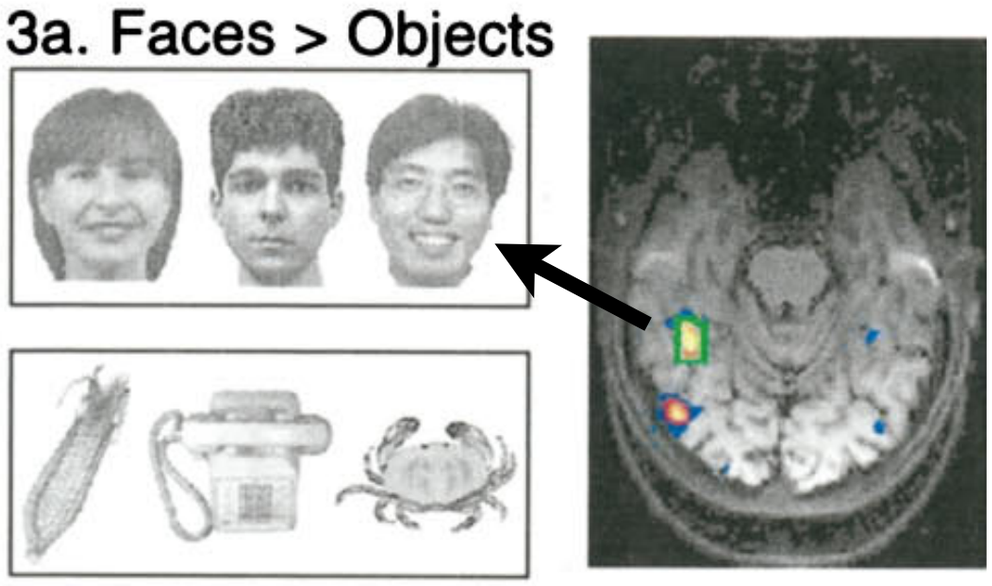



Scopus search: (“functional Magnetic Resonance Imaging” OR “functional MRI” OR “fMRI”) AND (((rest OR resting) AND connectivity) OR “resting state” OR “spontaneous fluctuations” OR “intrinsic fluctuations”)

Birn (2012) *NeuroImage*

# Paradigm shift

- Functionality: Local ⟶ Distributed



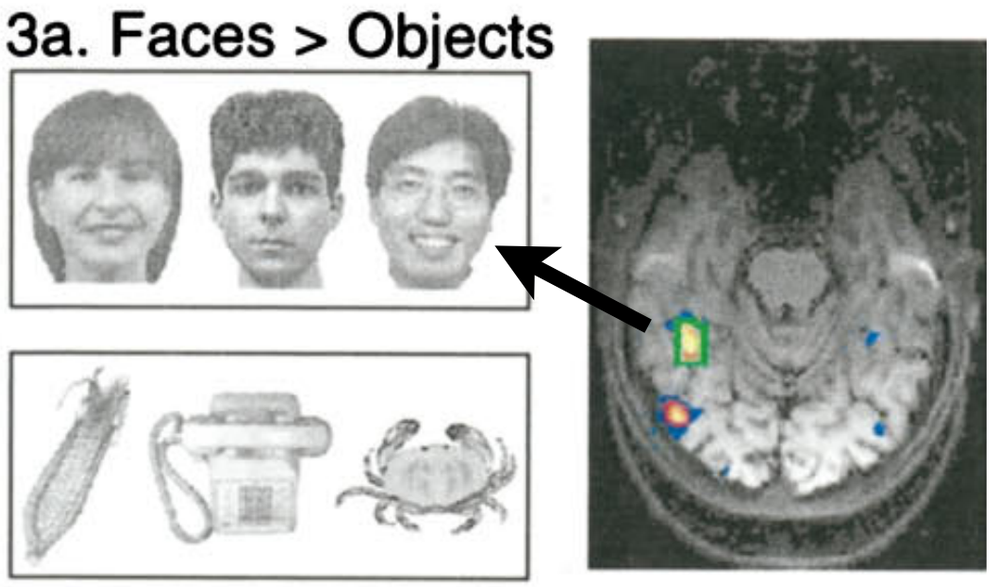




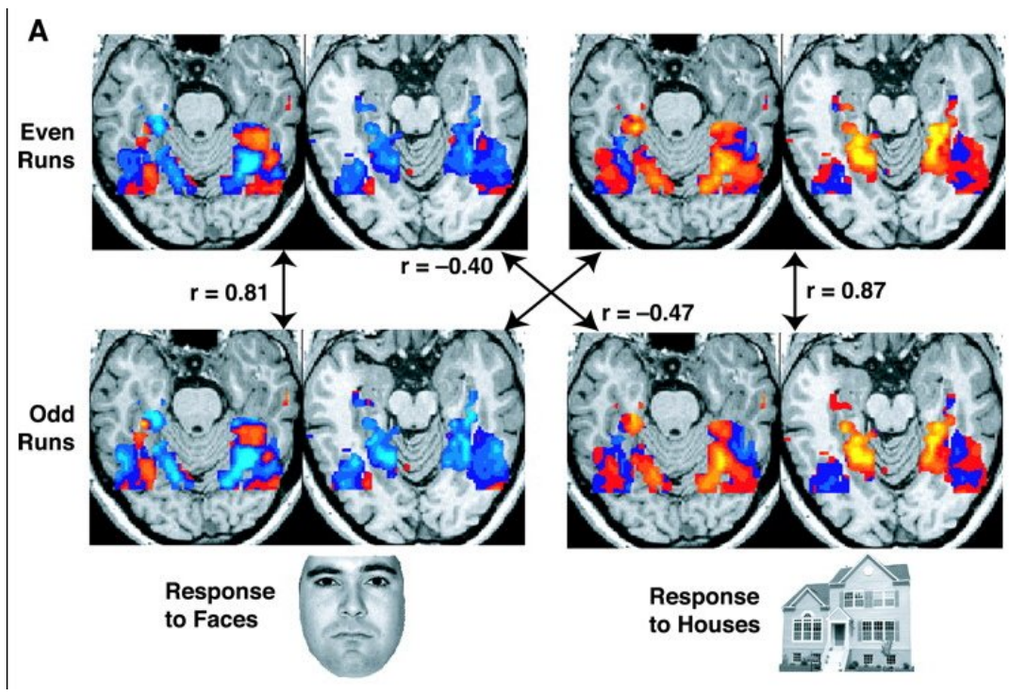
Kanwisher et al. (1997)
*J Neurosci*

# Paradigm shift

- Functionality: Local ⟶ Distributed




Kanwisher et al. (1997)
*J Neurosci*



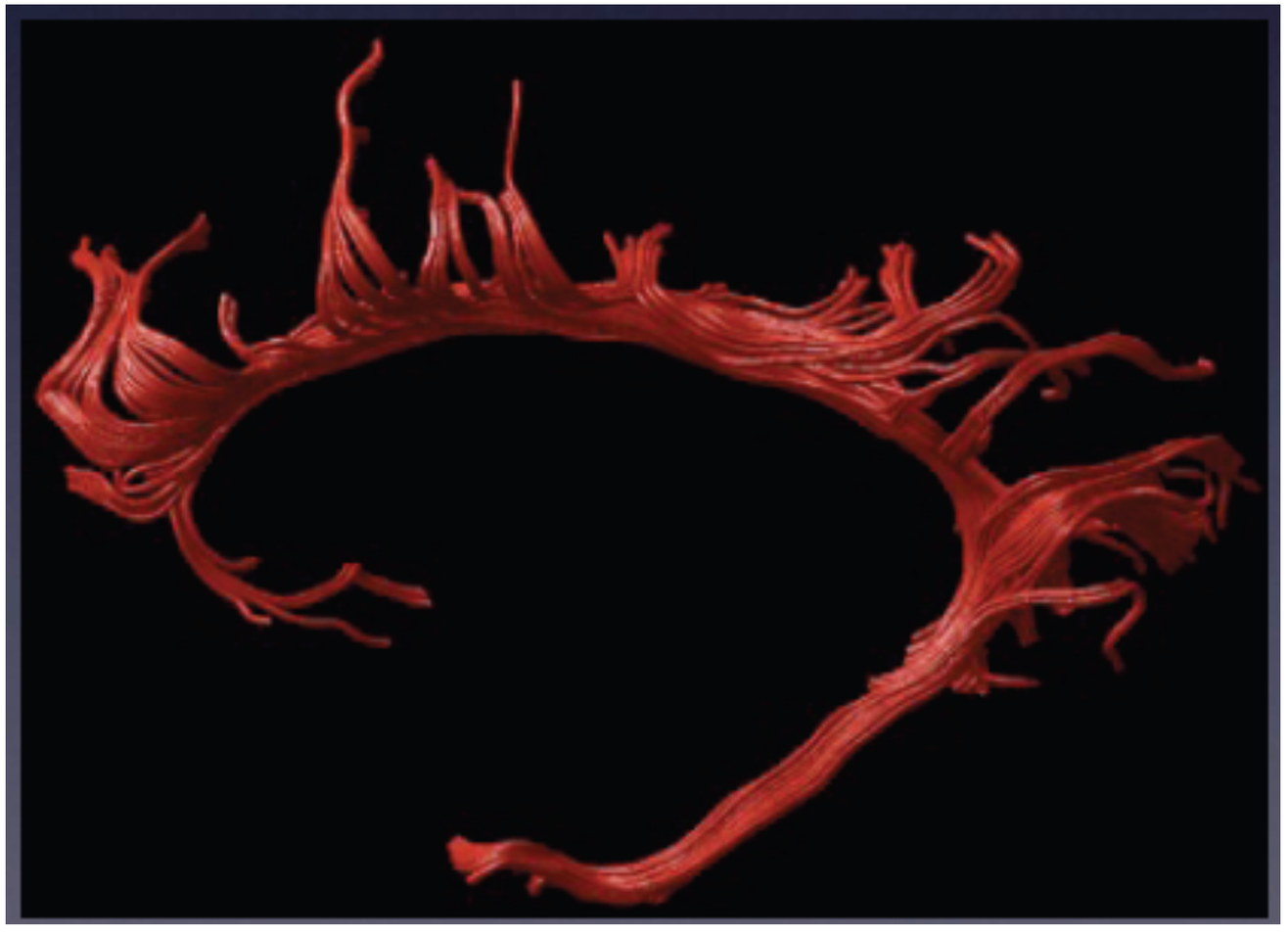

Haxby et al. (2001)
*Science*

# Paradigm shift

- Functionality: Local ⟶ Distributed
- How can we characterise systems?
- How can we characterise systems-level variability?
- Translational research; Clinic ⟷ Lab

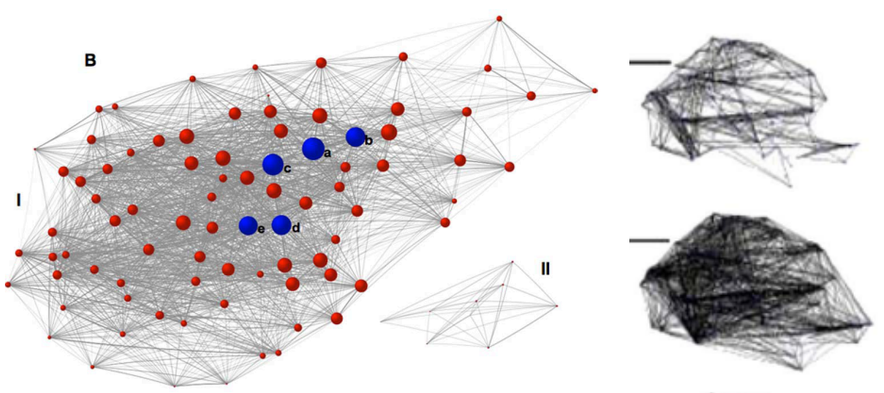
# Connectivity

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



# Functional connectivity (FC)

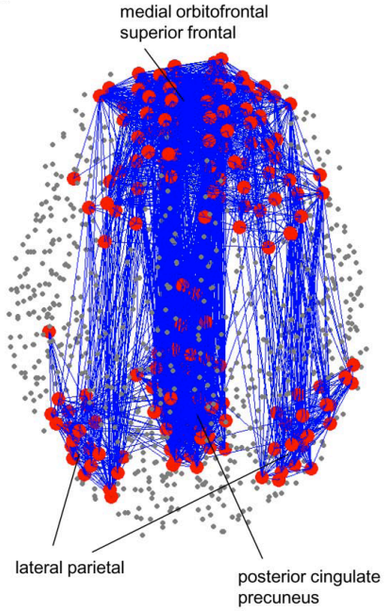
- "Temporal correlations between remote neurophysiological events" - Friston (1994), *HBM*



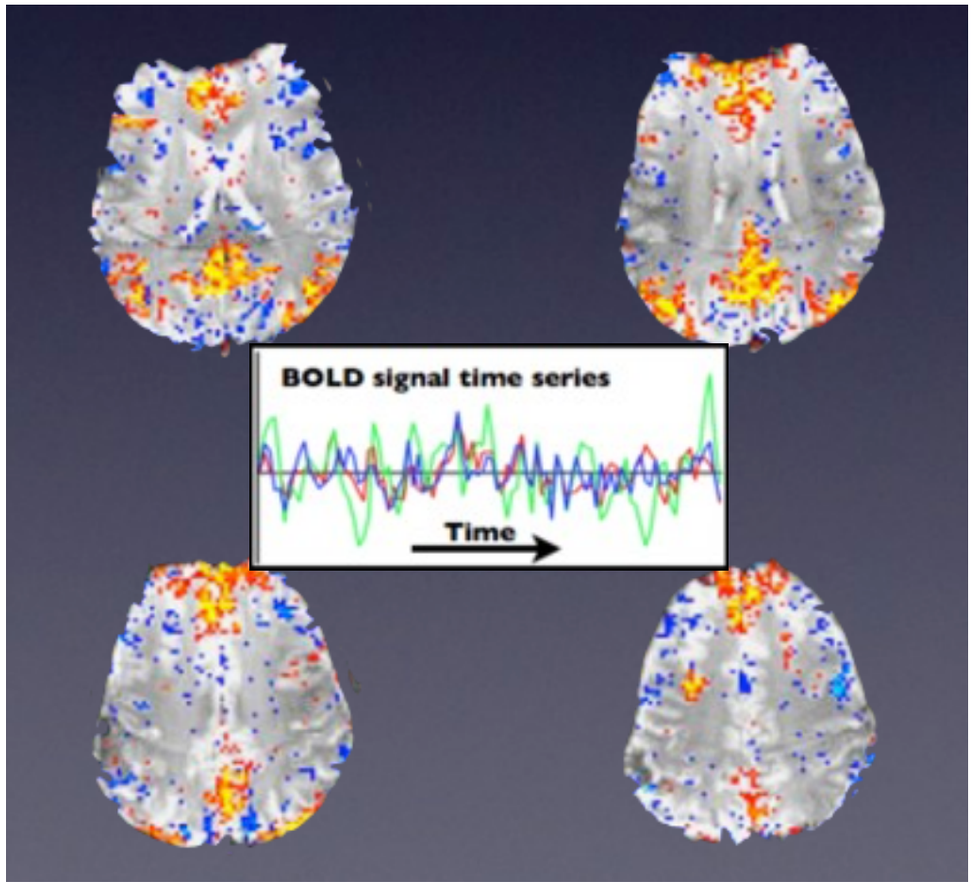

Buckner et al. '09 *J Neurosci*



Bullmore et al. '09 *Neuroimage*

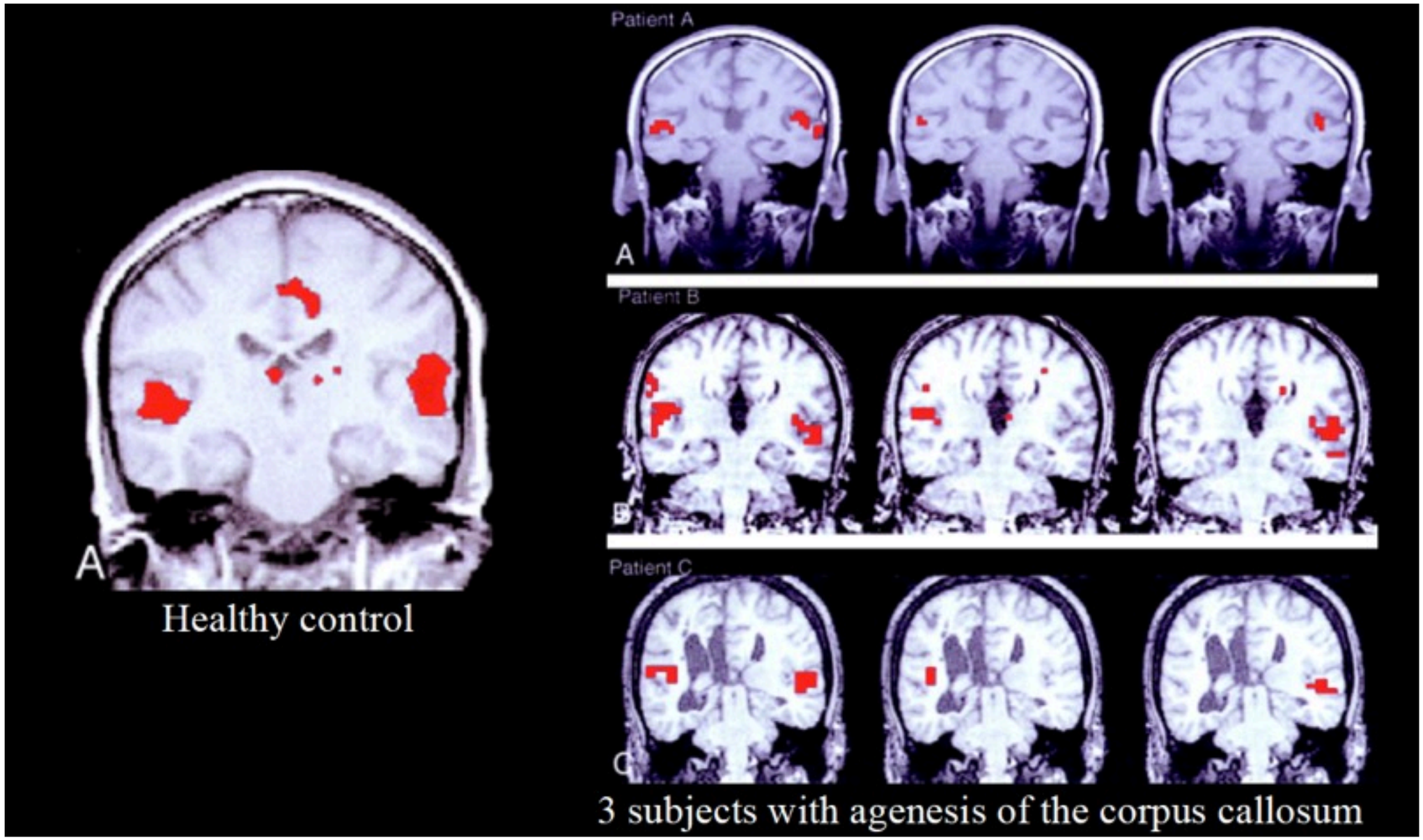



Honey et al. '09 *PNAS*



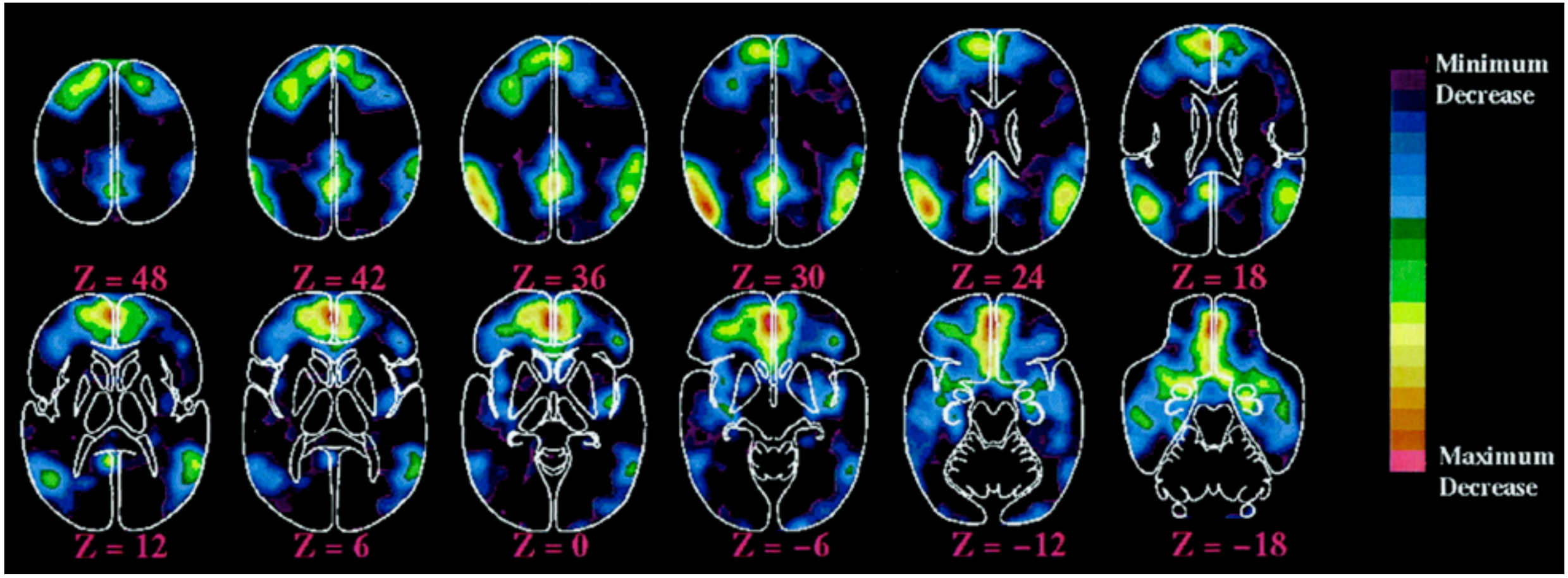

- Large-scale networks

# Connectivity: structural = functional?



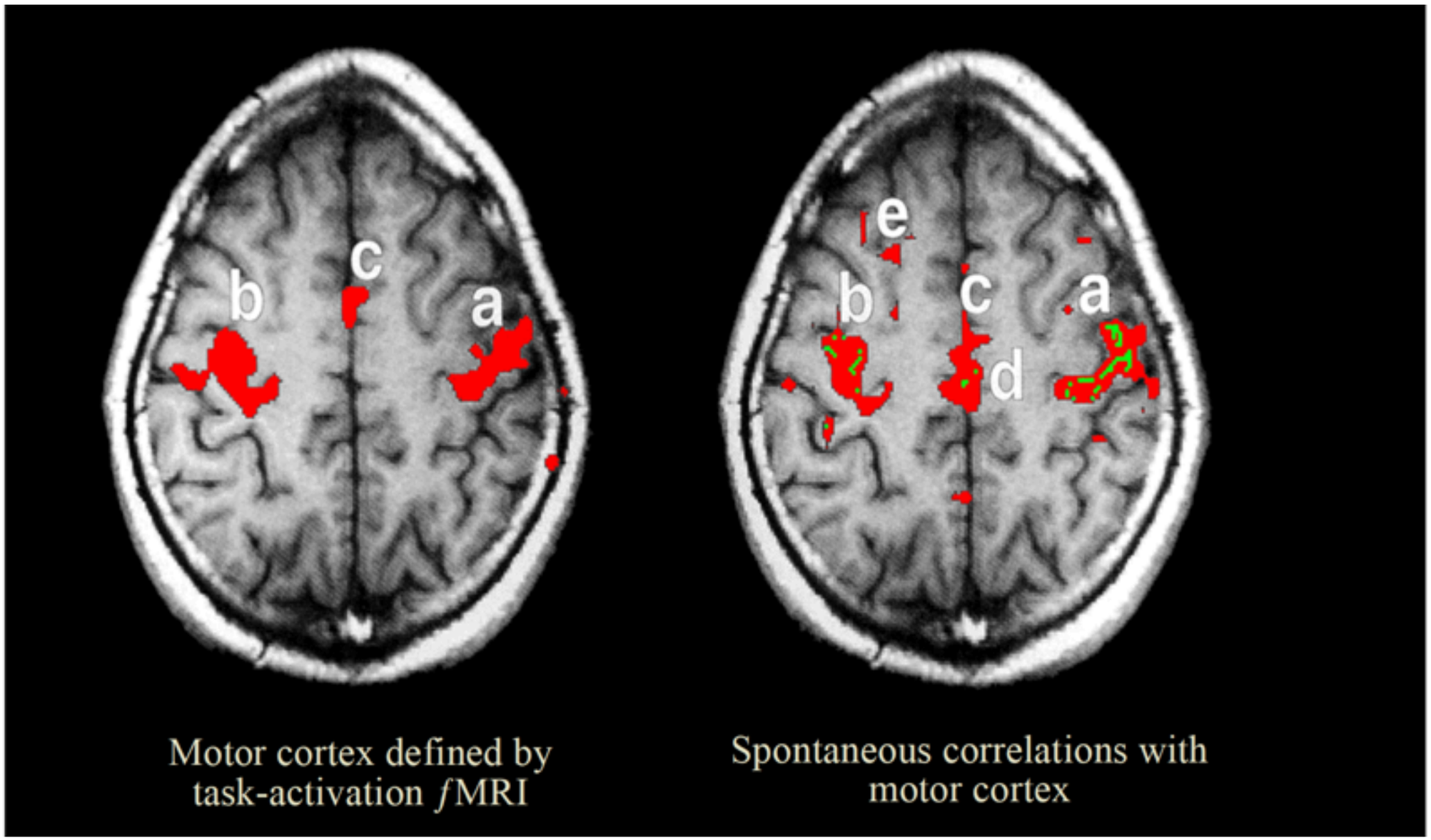

Quigley et al. (2003) *AJNR*

# This is not the activity you're looking for...



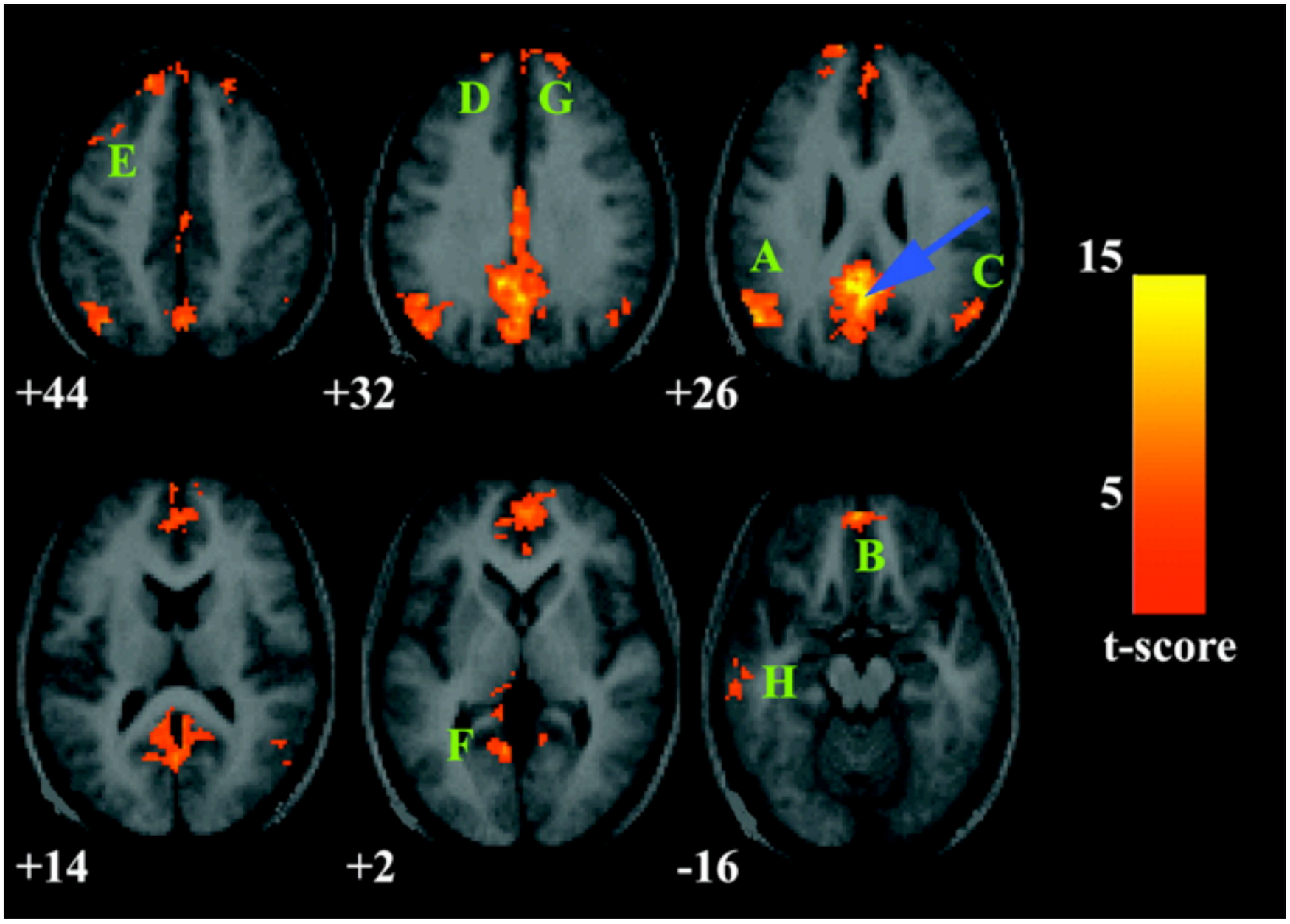

Shulman et al. (1997) *J Cogn Neurosci*; Raichle et al. (2001) *PNAS*

# Resting-state FC




Biswal et al. (1995) *Magn Reson Med*

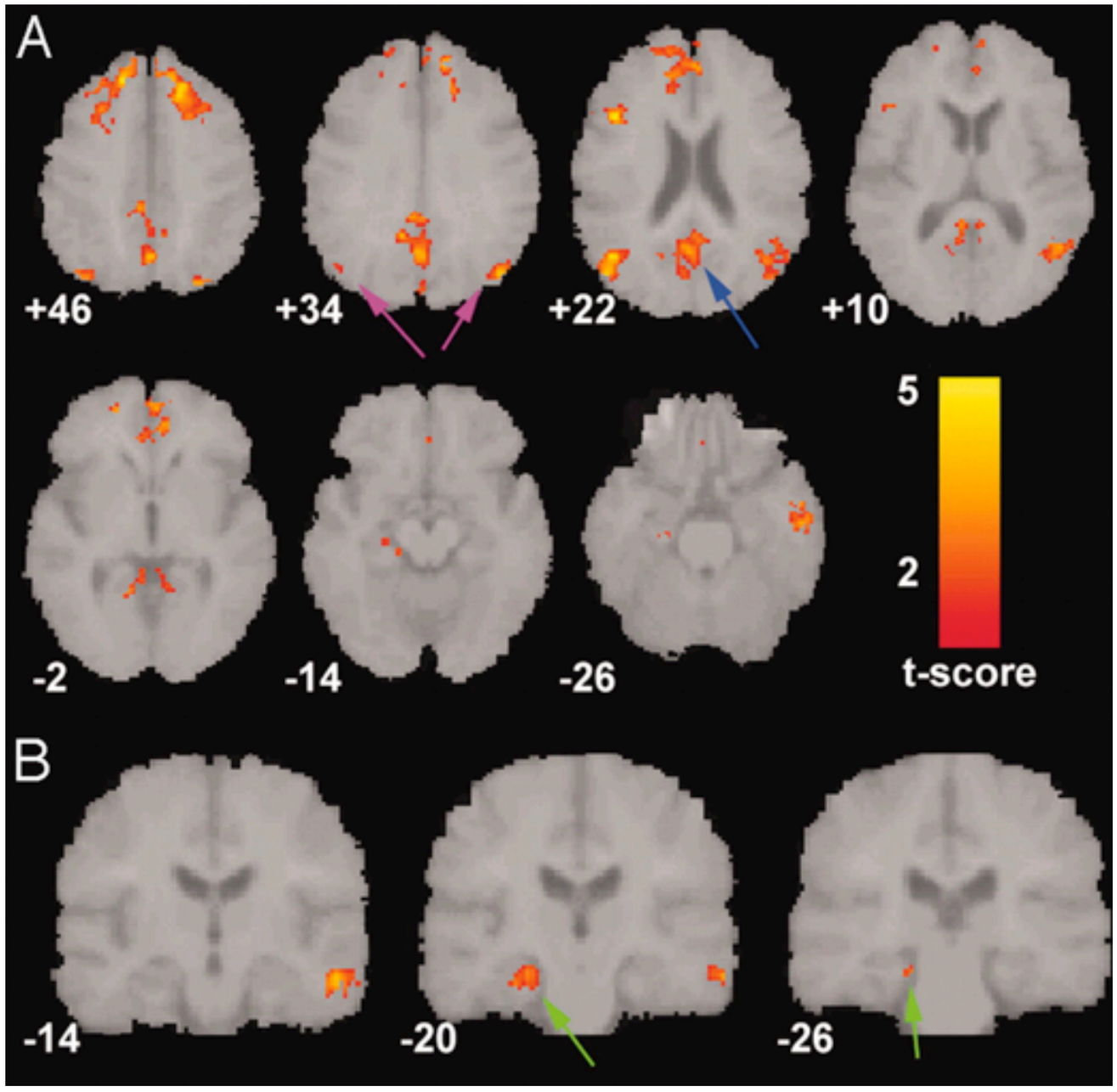
# Non-motor networks?




Greicius et al. (2003) *PNAS*

# Diseased networks?

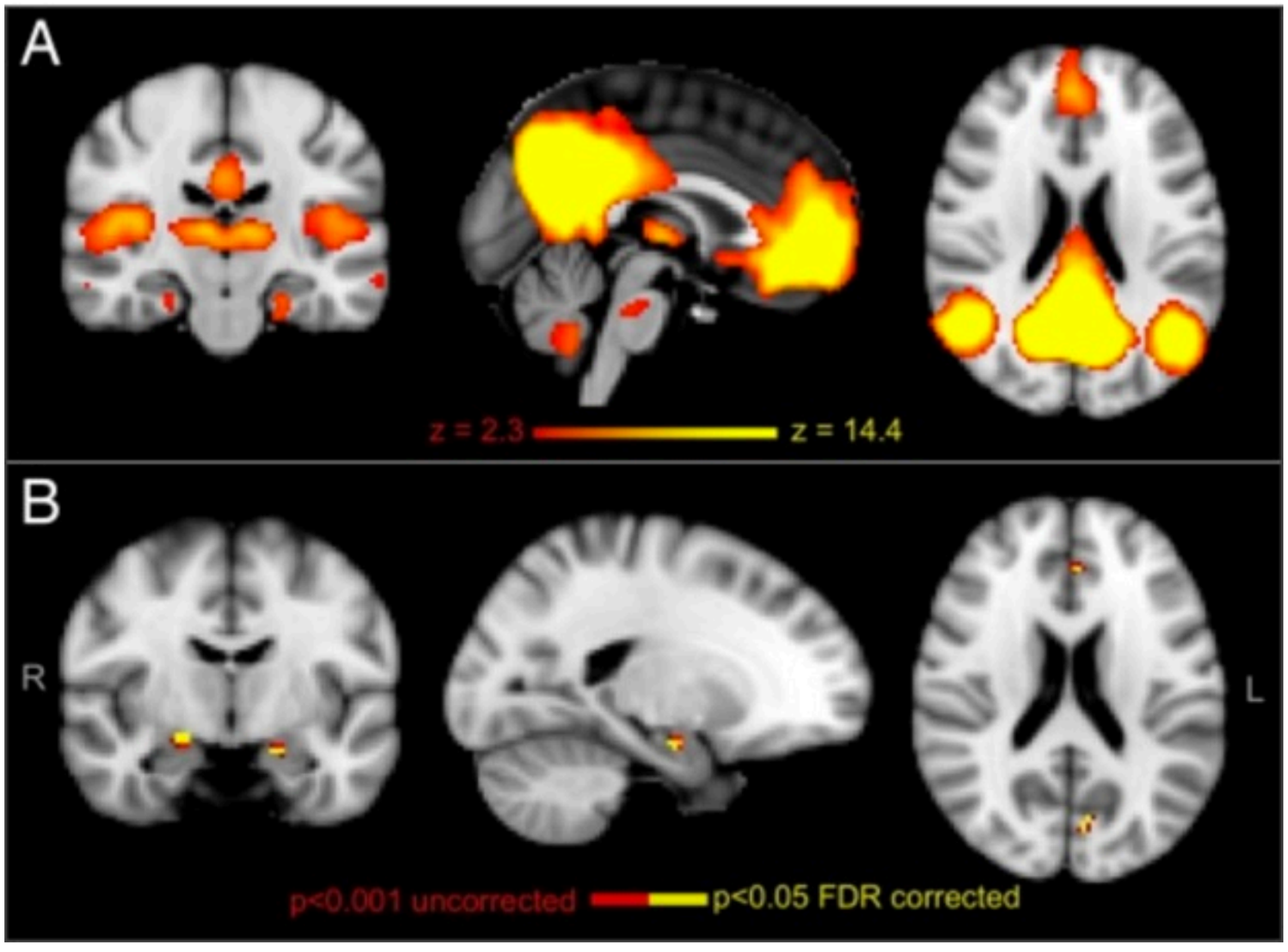
Healthy elderly > Alzheimer's




Greicius et al. (2004) *PNAS*

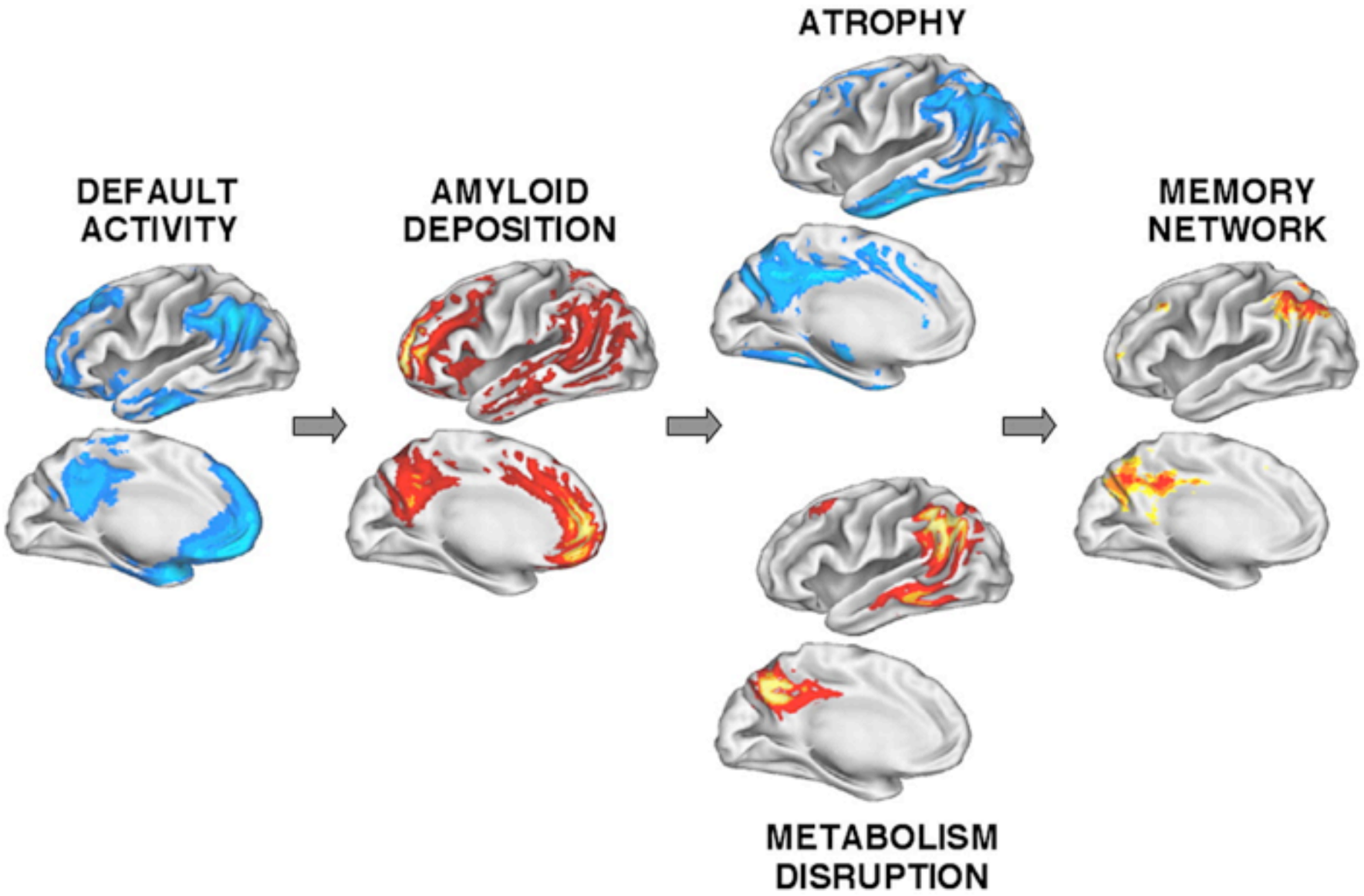
# Diseased networks?

Healthy, young, AD predisposed > non-predisposed



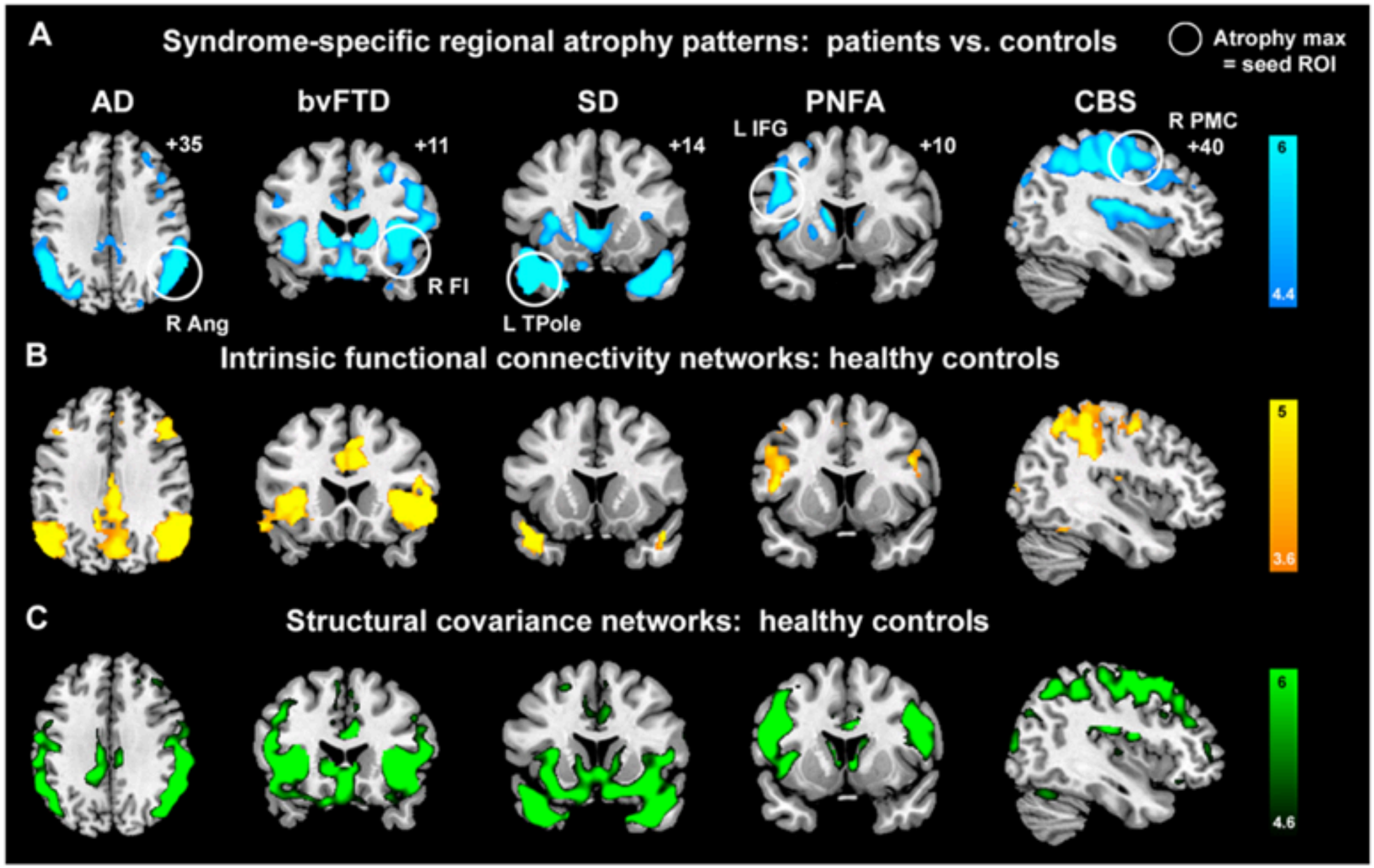

Filippini et al. (2009) *PNAS*

# 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?

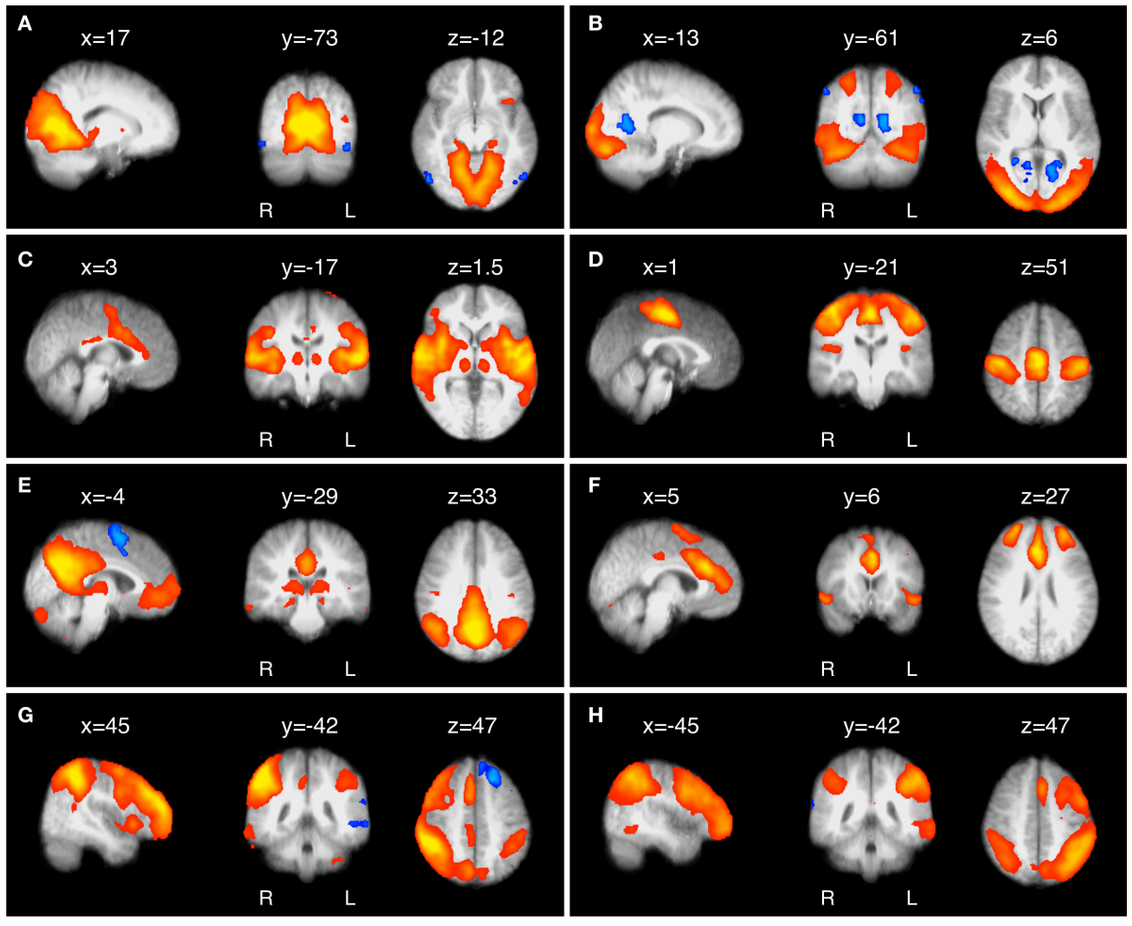
- A note on nomenclature...

| 1 | 2 |
|---|---|
| Resting(-state) | Connectivity |
| Intrinsic | Activity |
| Endogenous | Oscillations |
| Spontaneous | Fluctuations |
| Task-free/-independent | Magic etc. ... |

- "Resting-state" as a product of the method, not the interpretation

# Resting-state networks (RSNs)

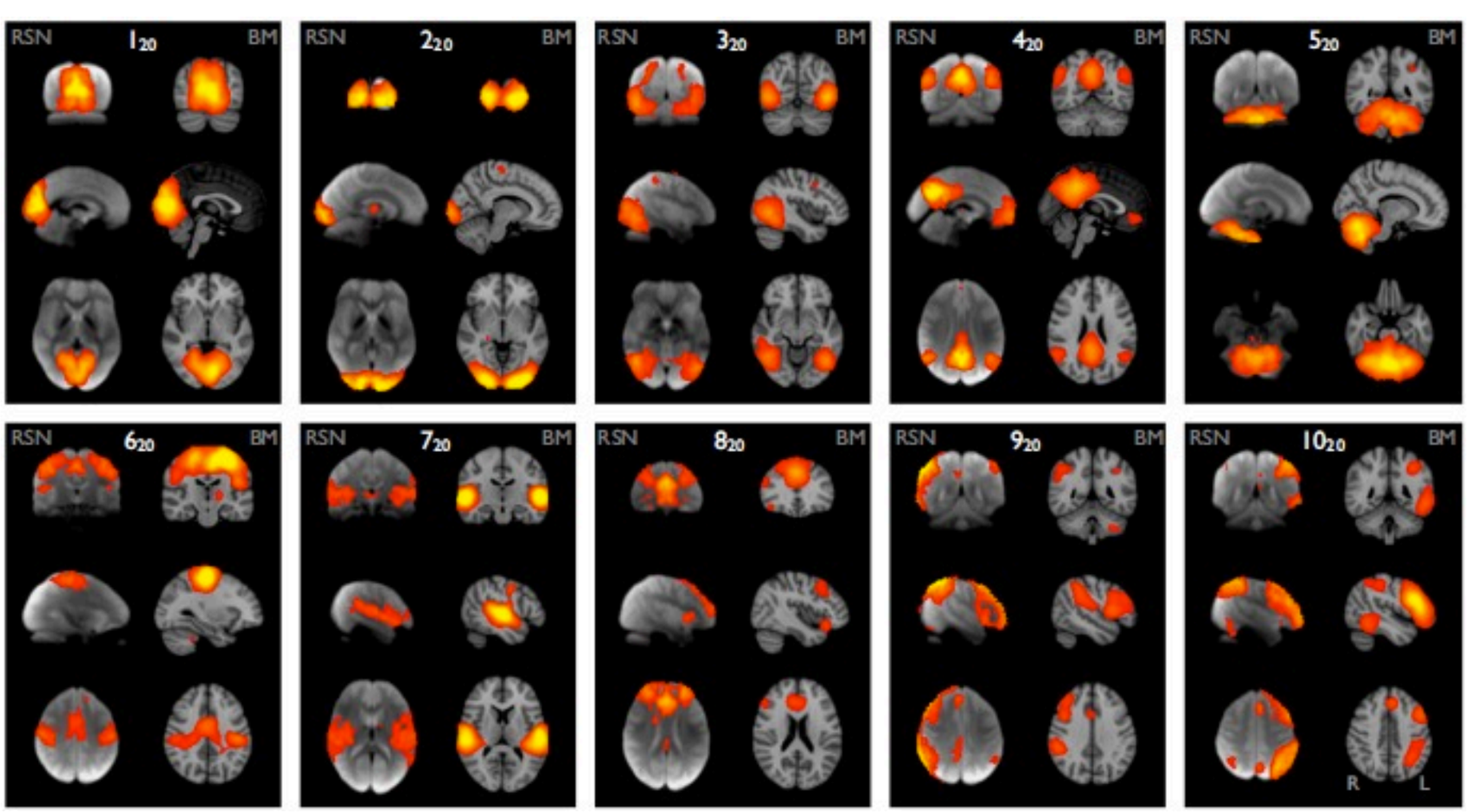
- Multiple spatial patterns of temporally correlated activity




Beckmann et al. (2005) *Phil Trans R Soc Lond B*

# Resting-state networks (RSNs)

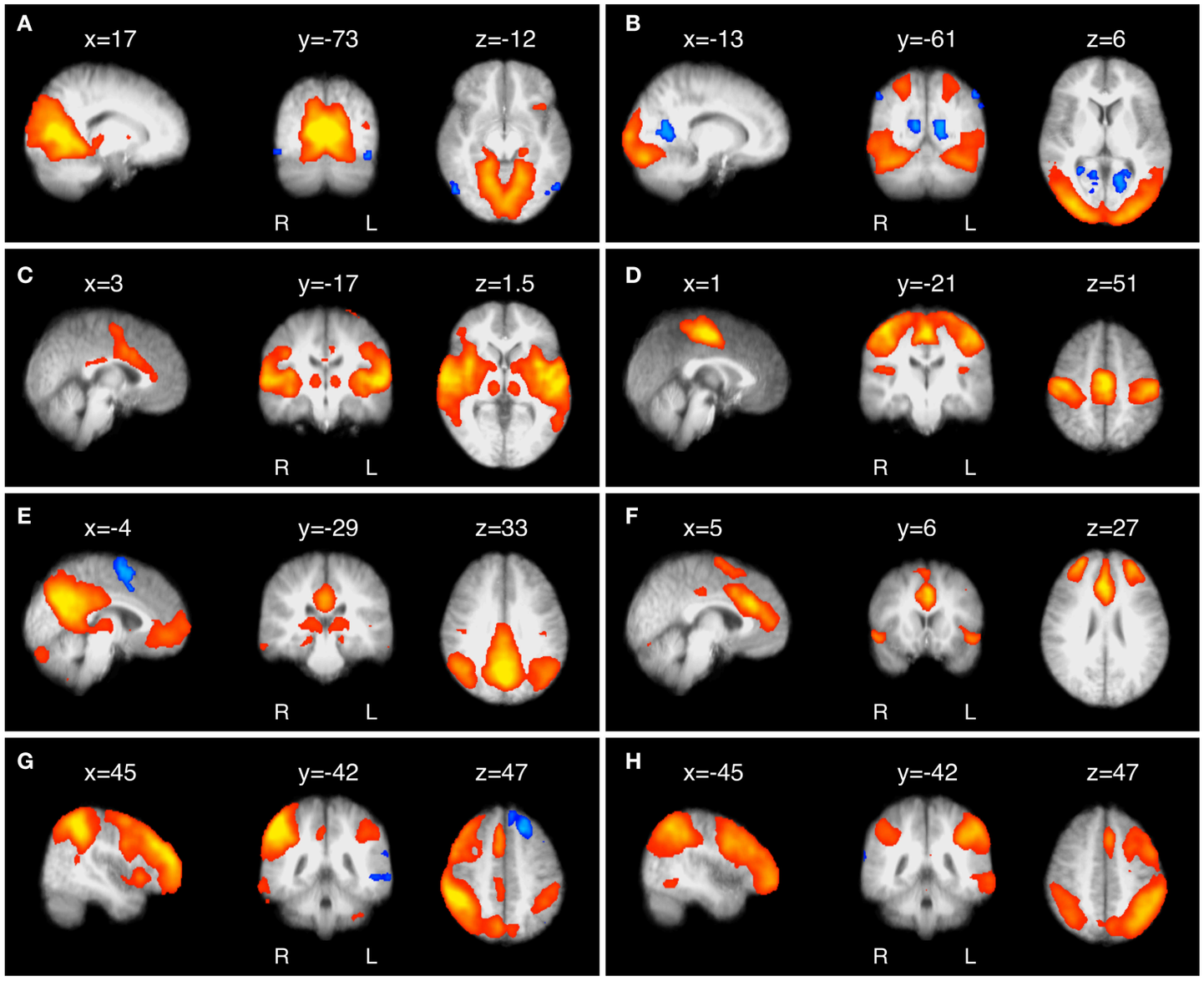
- Multiple spatial patterns of temporally correlated activity
- RSNs reflect distinct, large-scale neuronal functional systems
- Can be identified in absence of strictly-defined models




Smith et al. (2009)
*PNAS*

# Resting-state networks (RSNs)

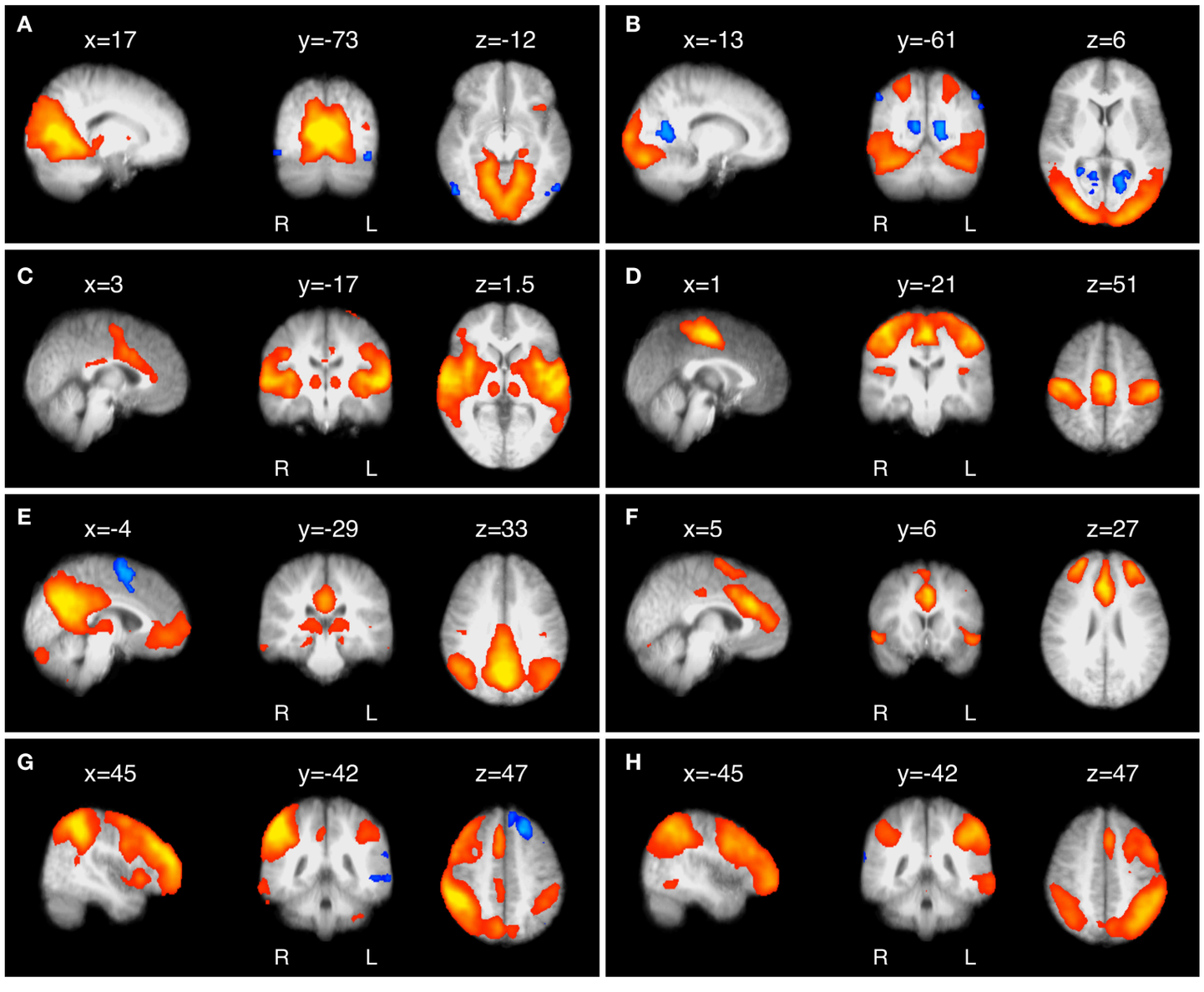
- Spatial characteristics:

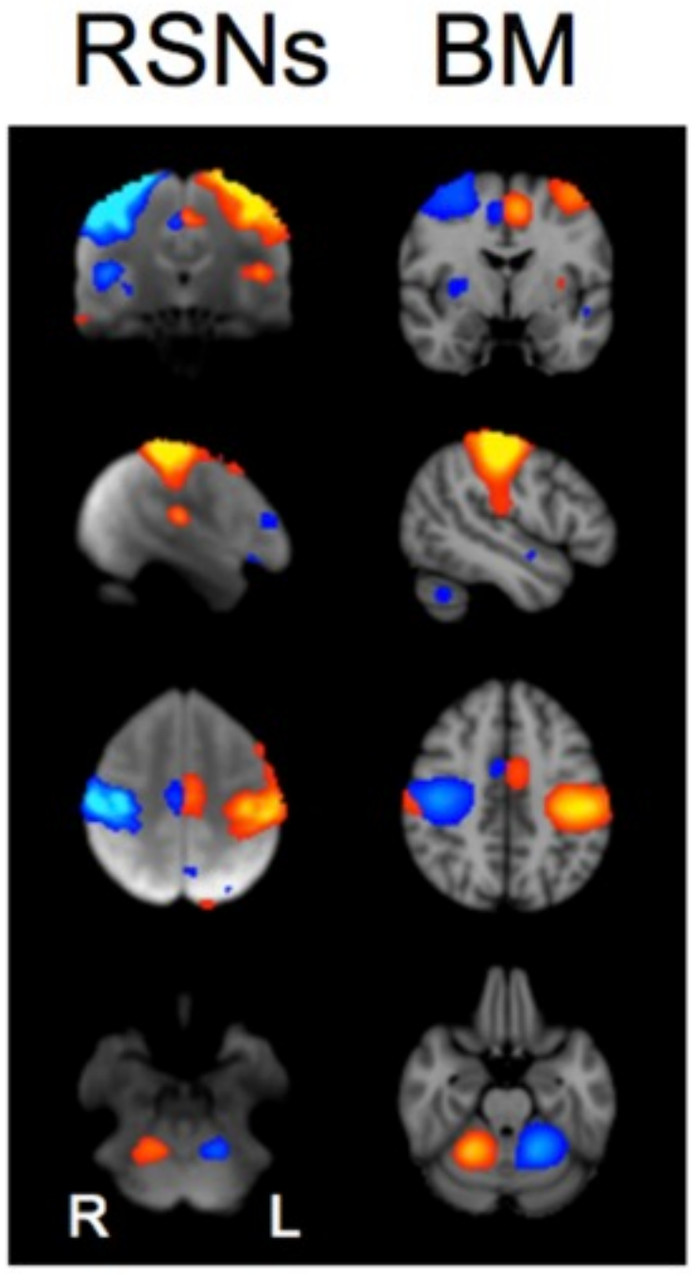



Beckmann et al. (2005) *Phil Trans R Soc Lond B*

# Resting-state networks (RSNs)

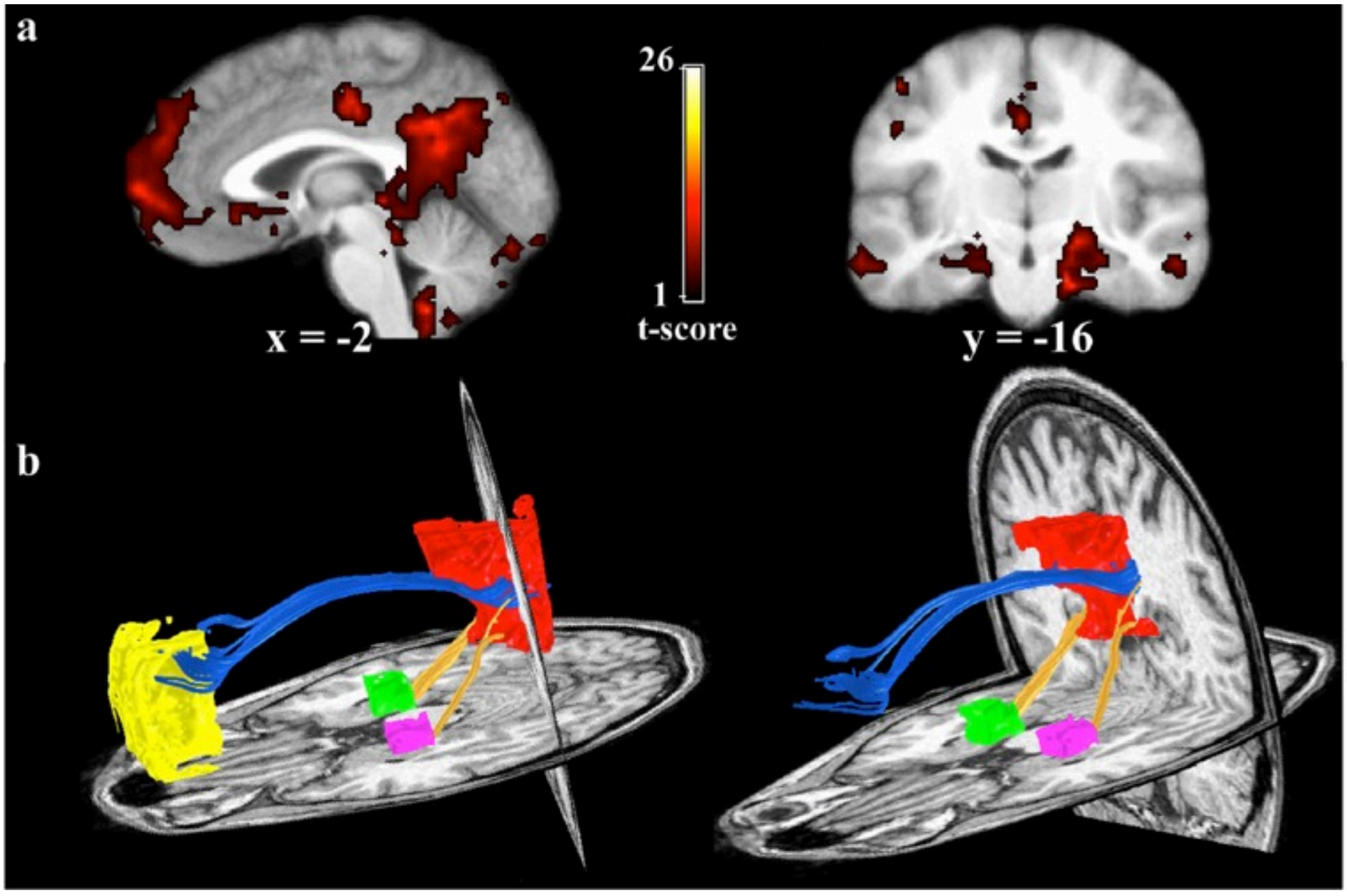
- Spatial characteristics: (dys)function?



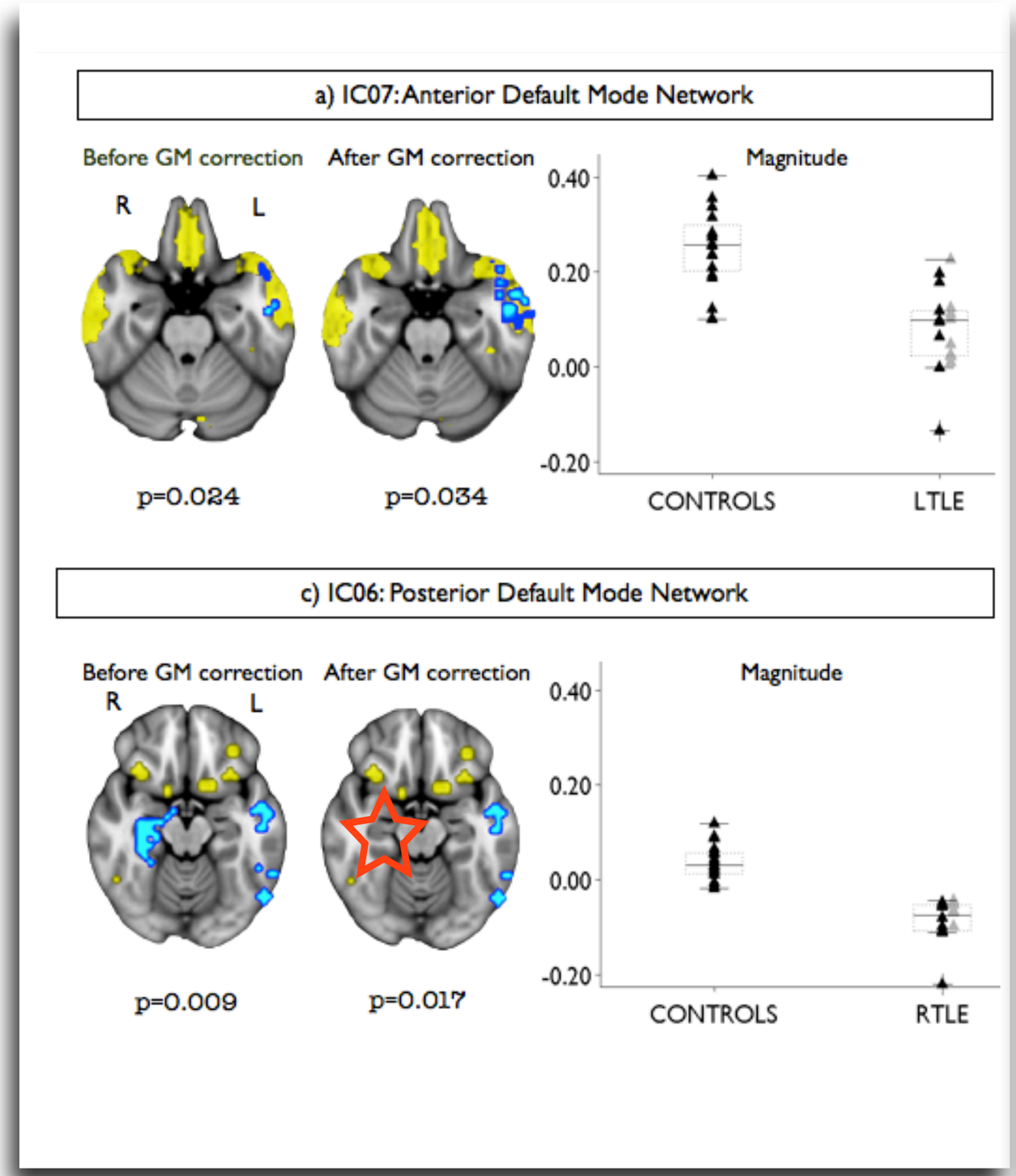

Smith et al. (2009)
*PNAS*

# RSN connectivity: structural = functional

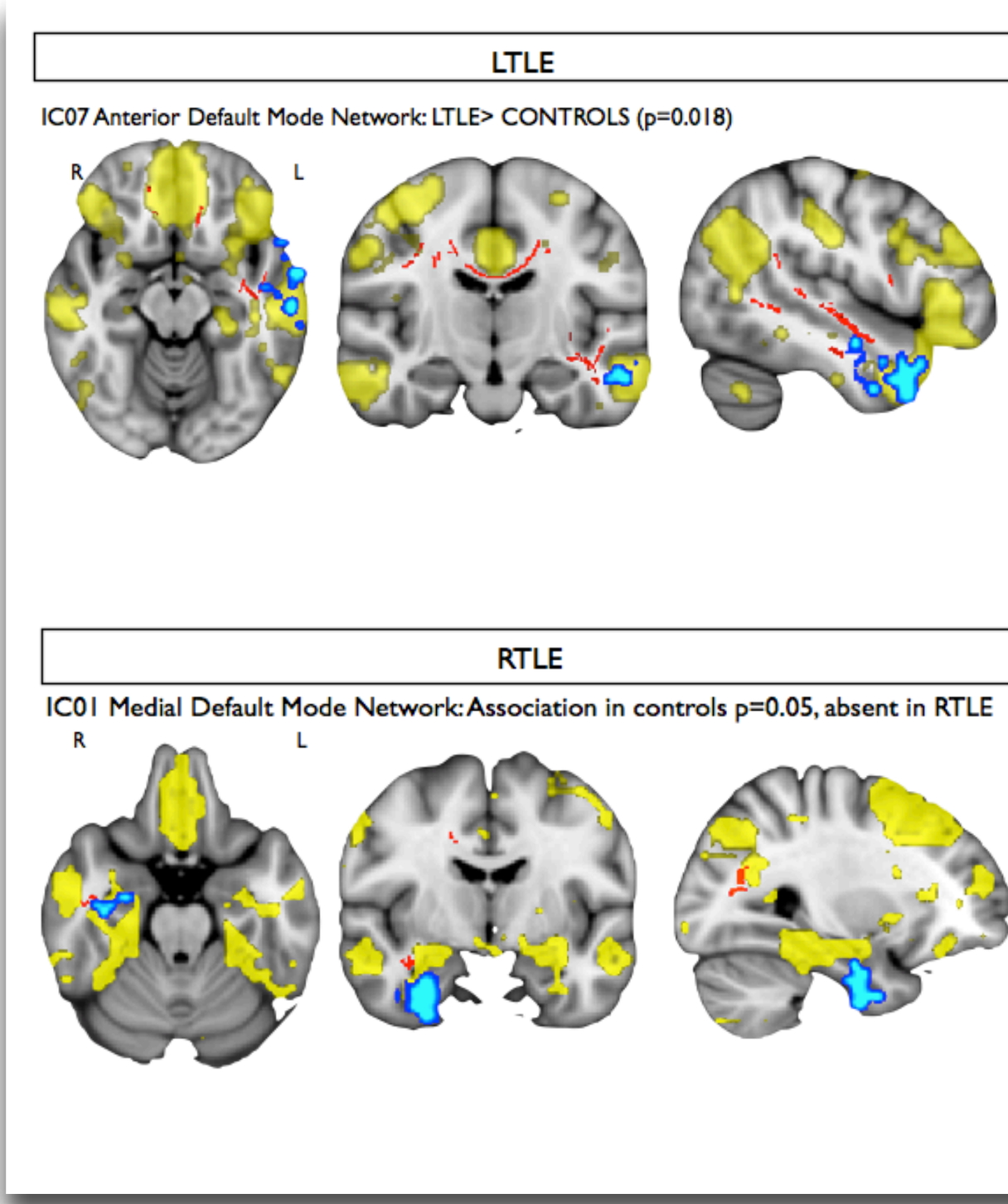



Greicius et al. (2008) *Cereb Cortex*

## Grey Matter Density Confound



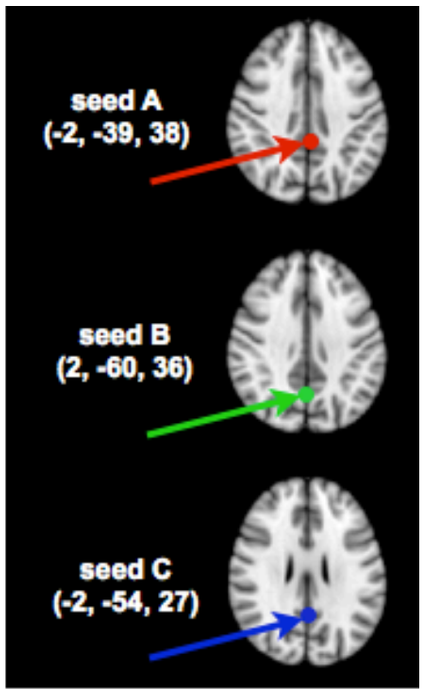

## Correlation with white matter structure



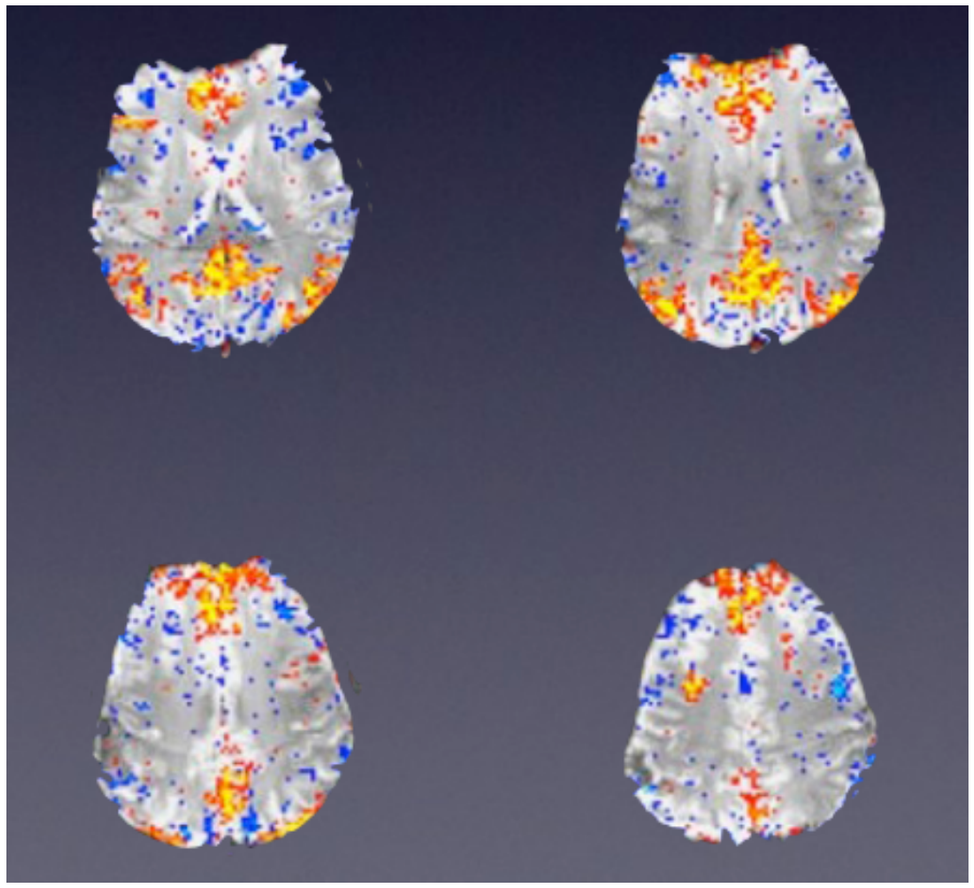

Voets et al. (2012) *Brain*

# Resting-state FC analysis options

1. Seed-based correlation analysis (SCA)

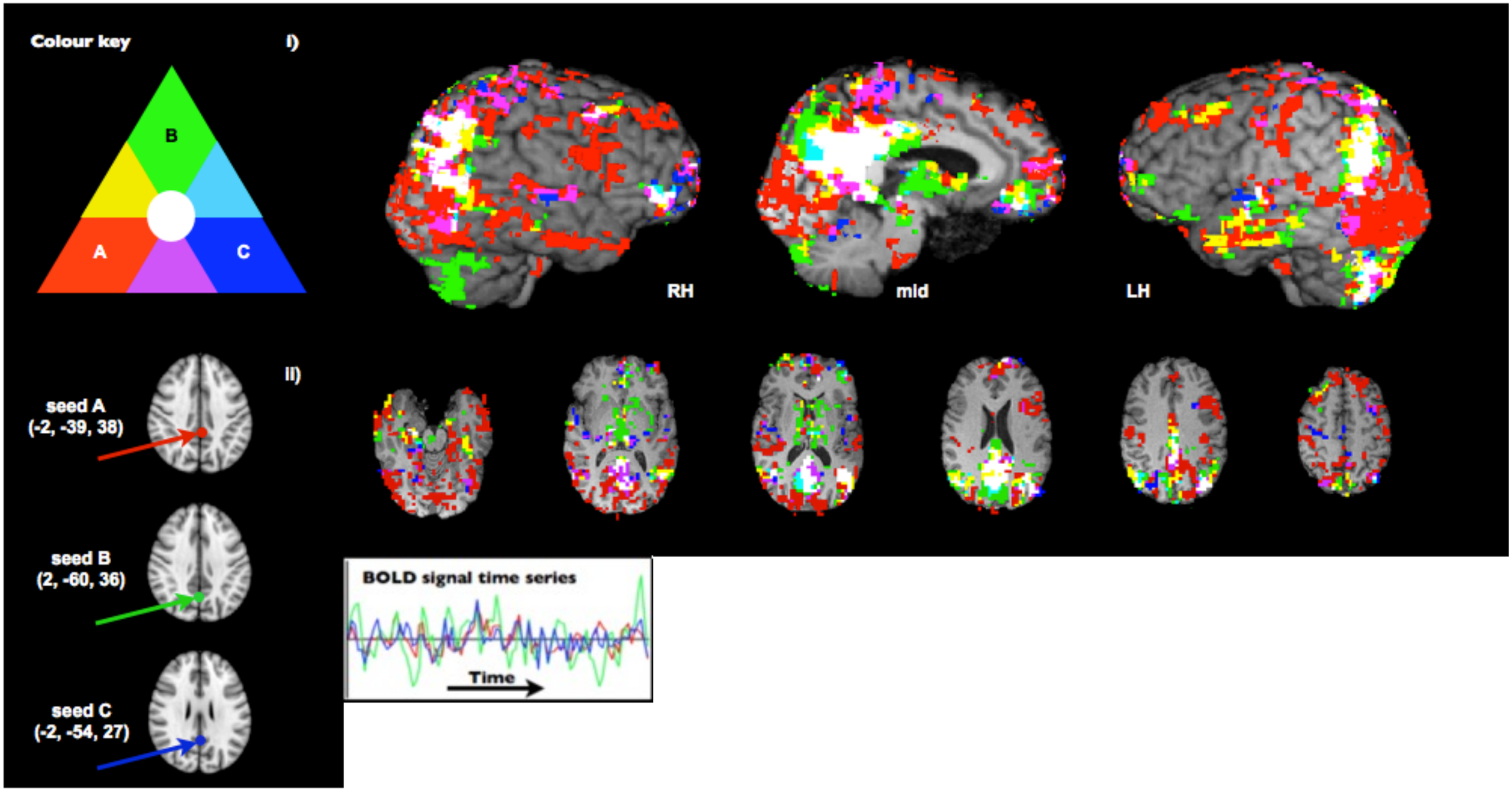



2. Independent component analysis (ICA)



3. Psycho-/physio-physiological interaction (PPI) analysis?

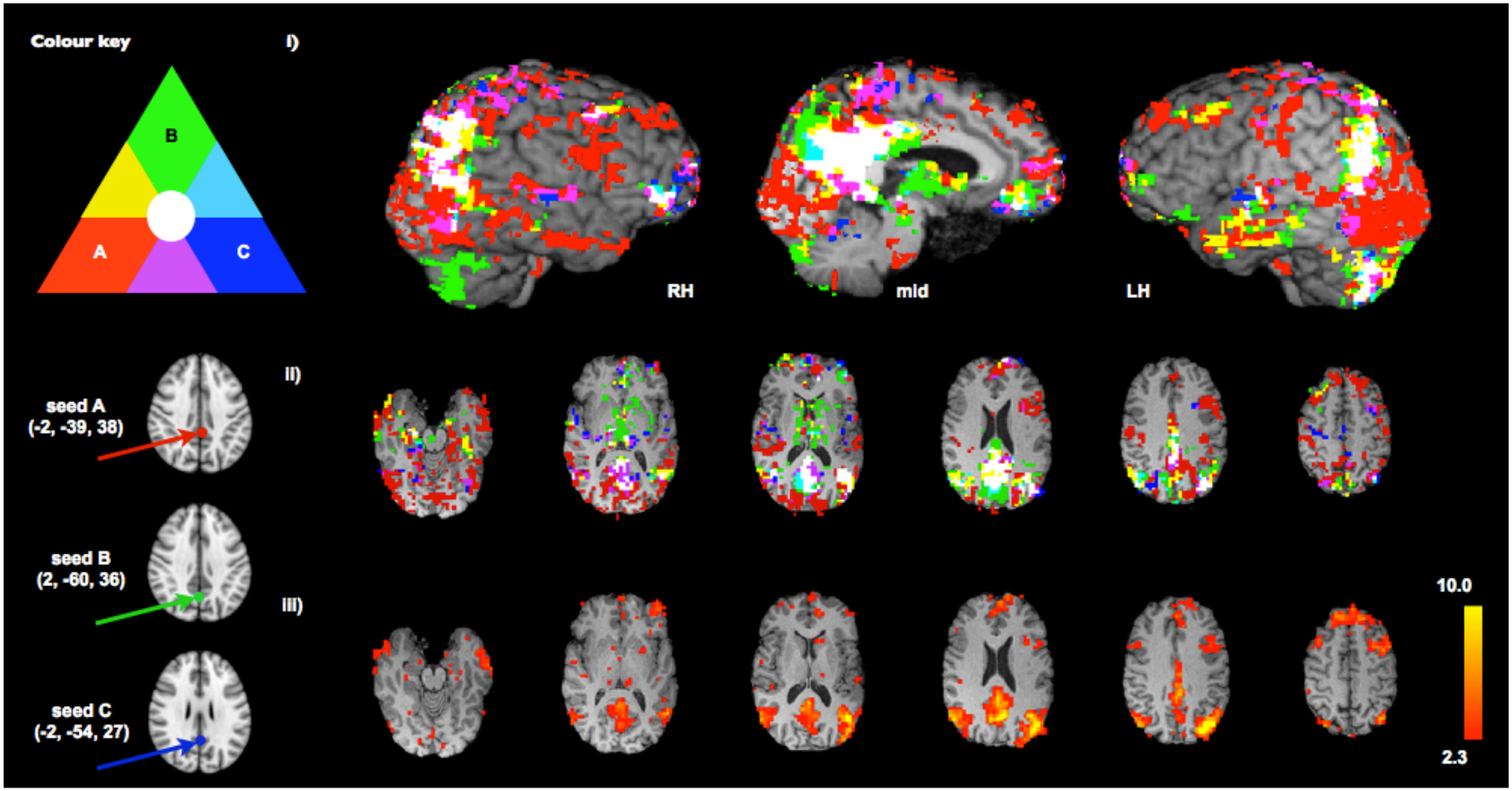
# Analysis pros & cons: SCA




Cole et al. (2010)
*Front Syst Neurosci*

1. Seed-based correlation analysis: 'mass univariate' approach

# Analysis pros & cons: SCA




Cole et al. (2010)
*Front Syst Neurosci*

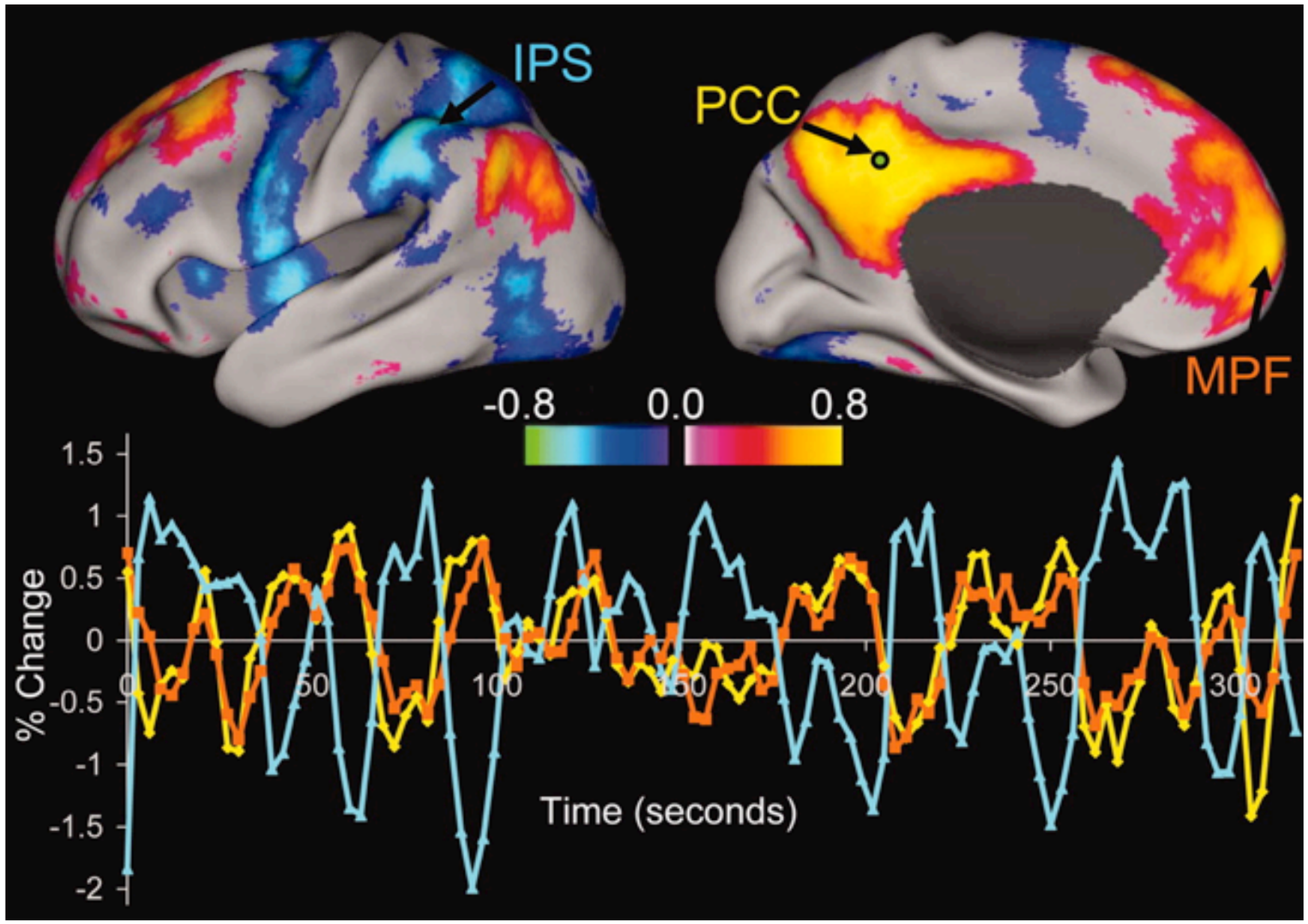
2. Independent component analysis: ‘multivariate’ approach

# 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

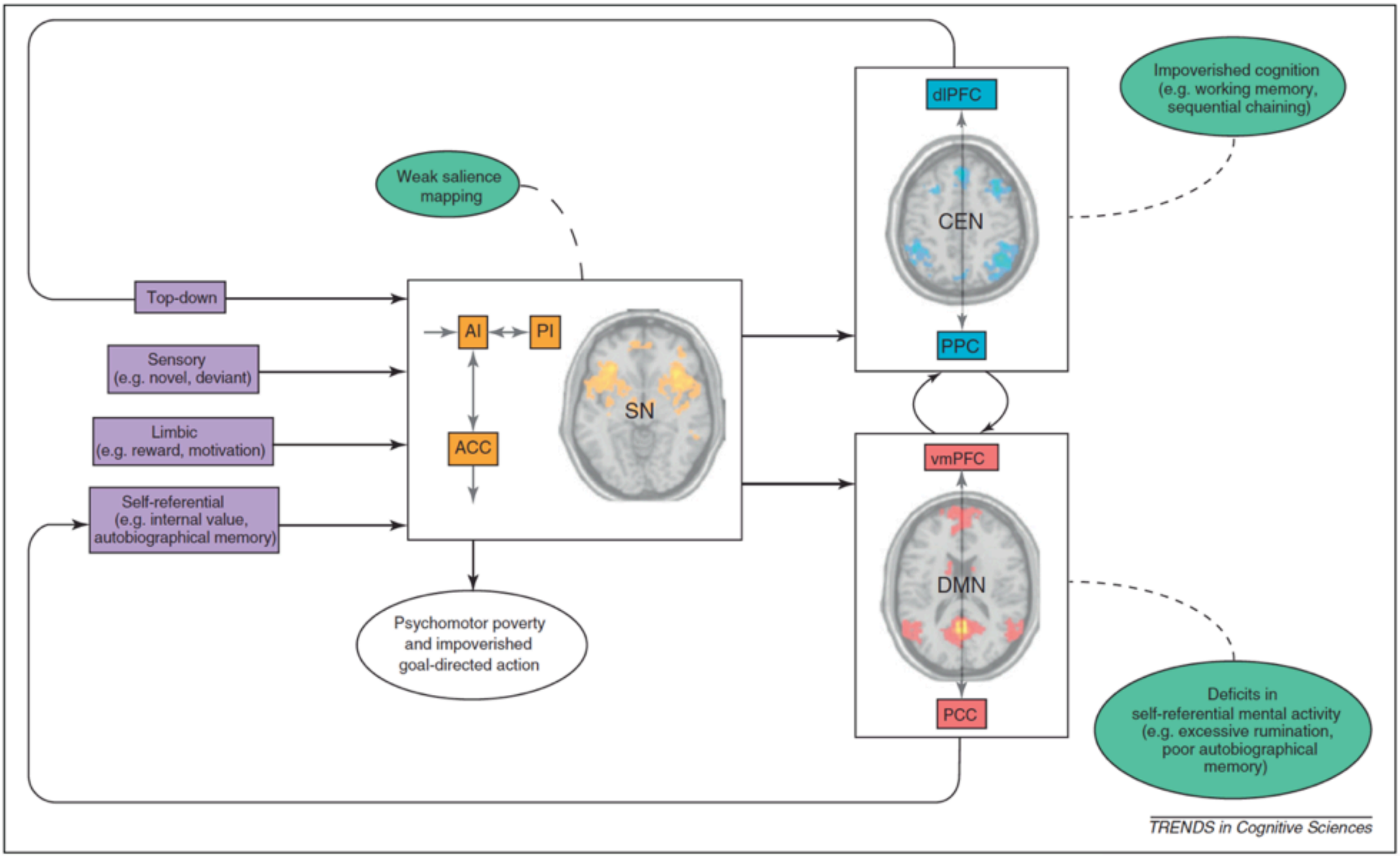
# Between-network interactions

- RSN temporal characteristics (e.g., 'nonstationarity')?




Fox et al. (2005)
*PNAS*

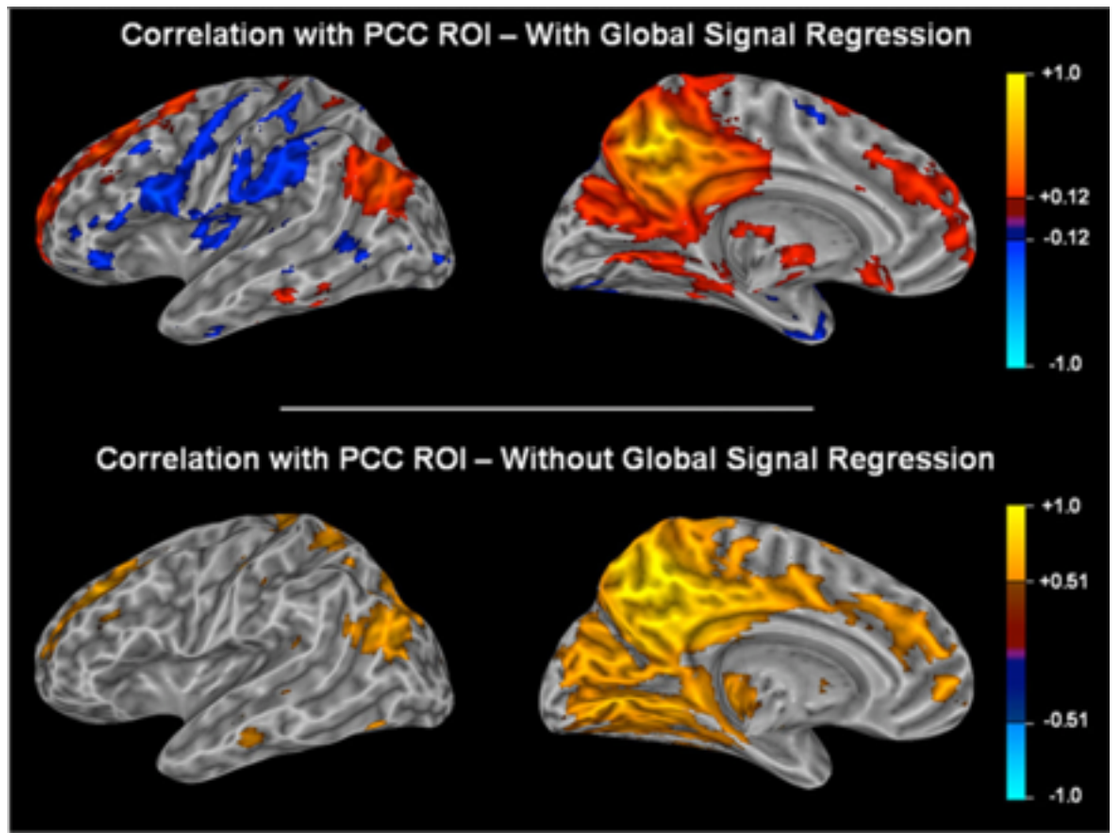
# Between-network psychopathology model




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)

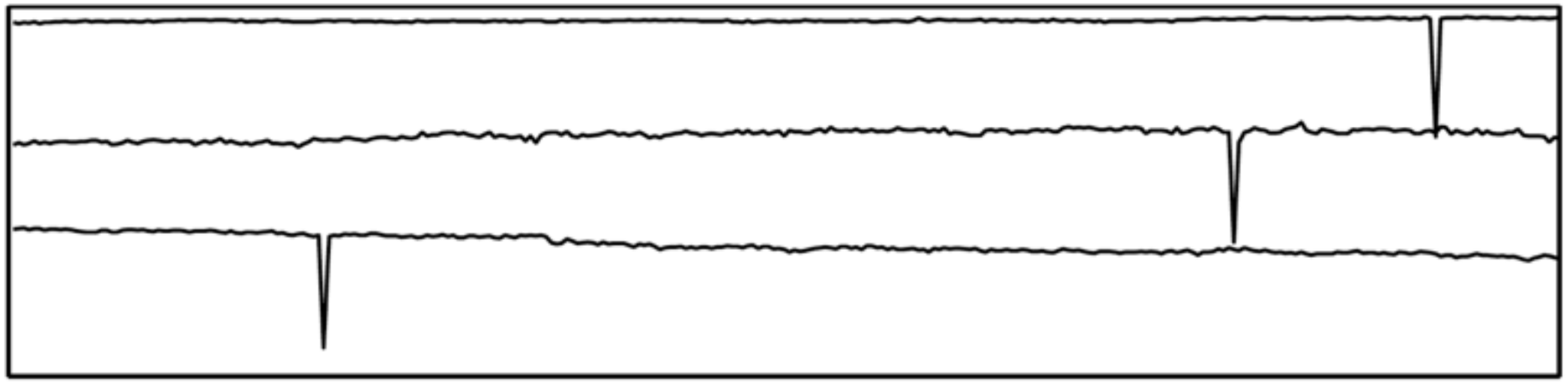
- Finds projections (components) of maximal independence in non-Gaussian data using higher-order (multivariate) statistics
- Multiple software packages for applying ICA to fMRI
  - FSL MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components)
  - GIFT
  - ICASSO... etc.

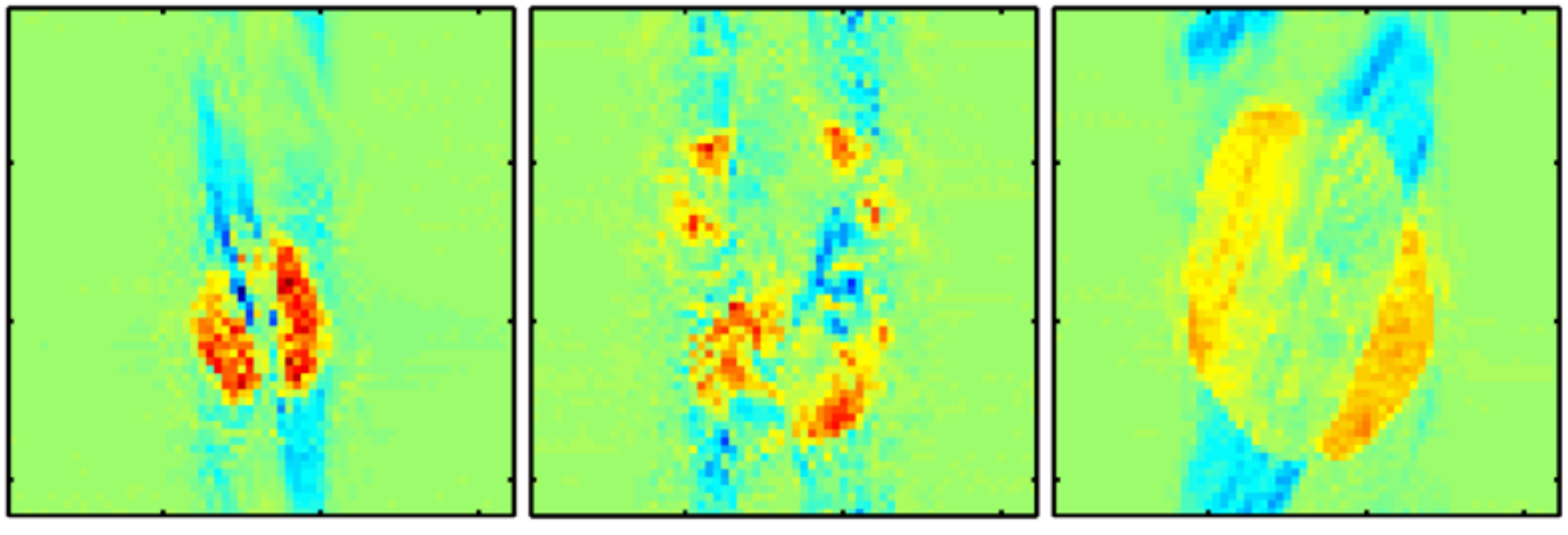
# Analysis pros & cons: ICA

- 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’

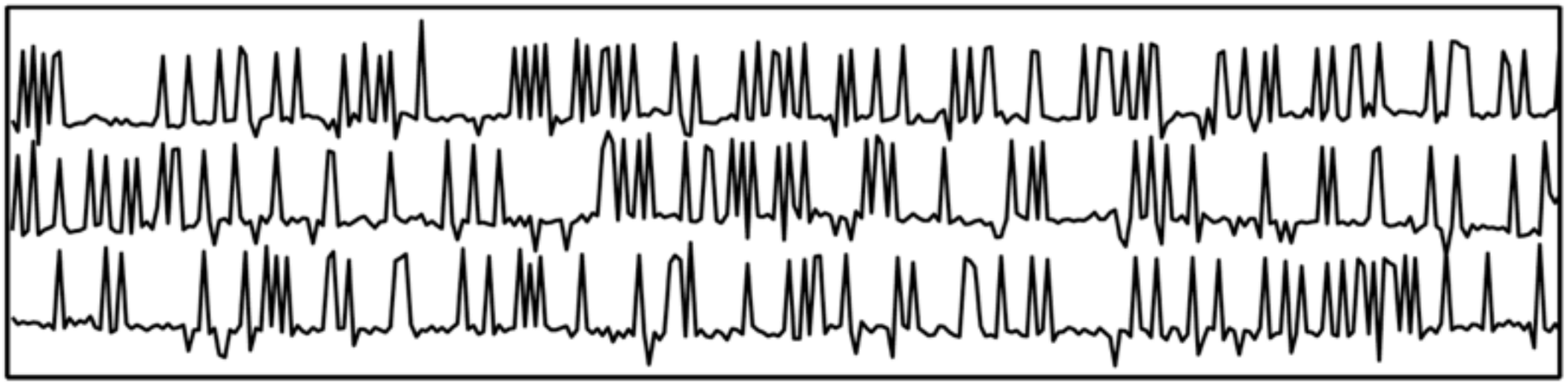


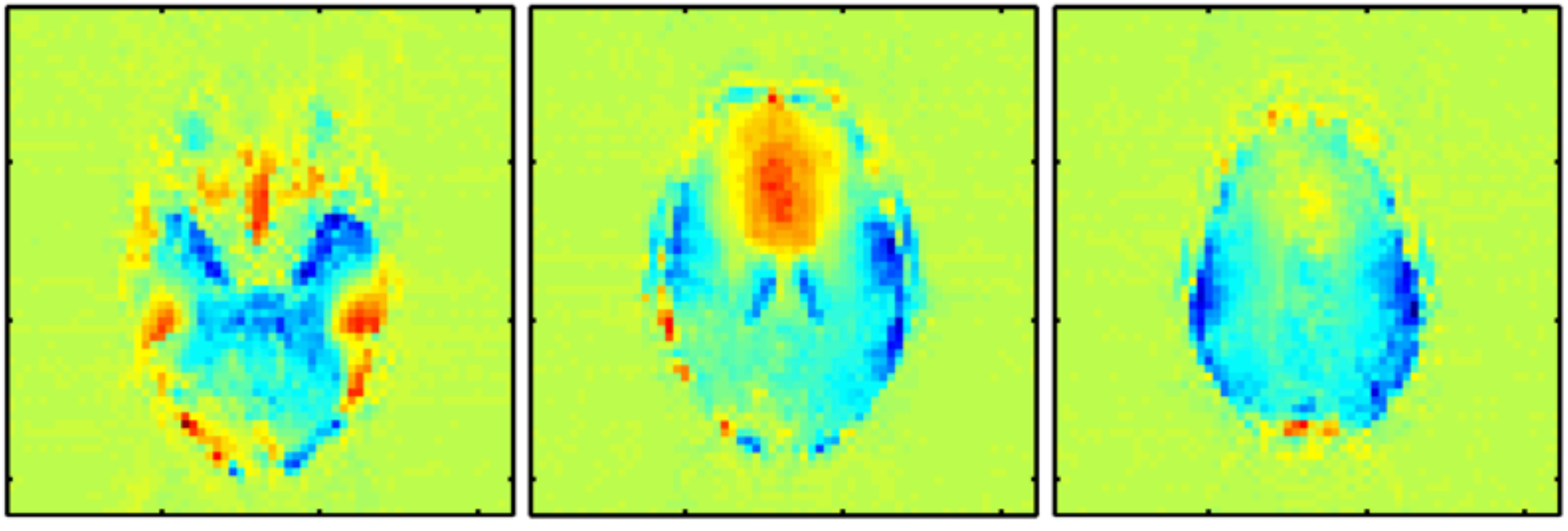


Thanks to C. Beckmann for examples

# Analysis pros & cons +

- Noise components
- gradient instability

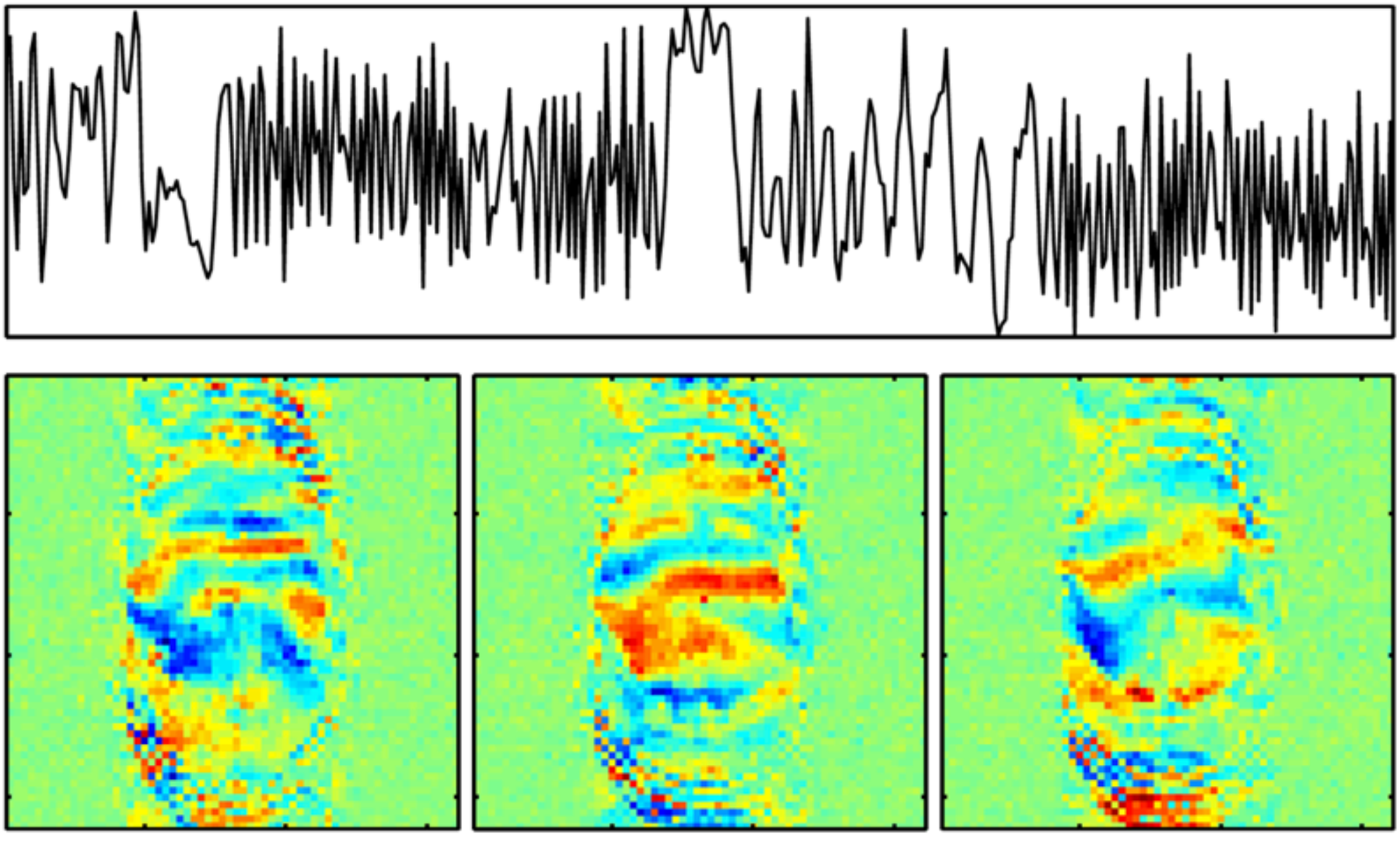




Thanks to C. Beckmann for examples

# Analysis pros & cons +

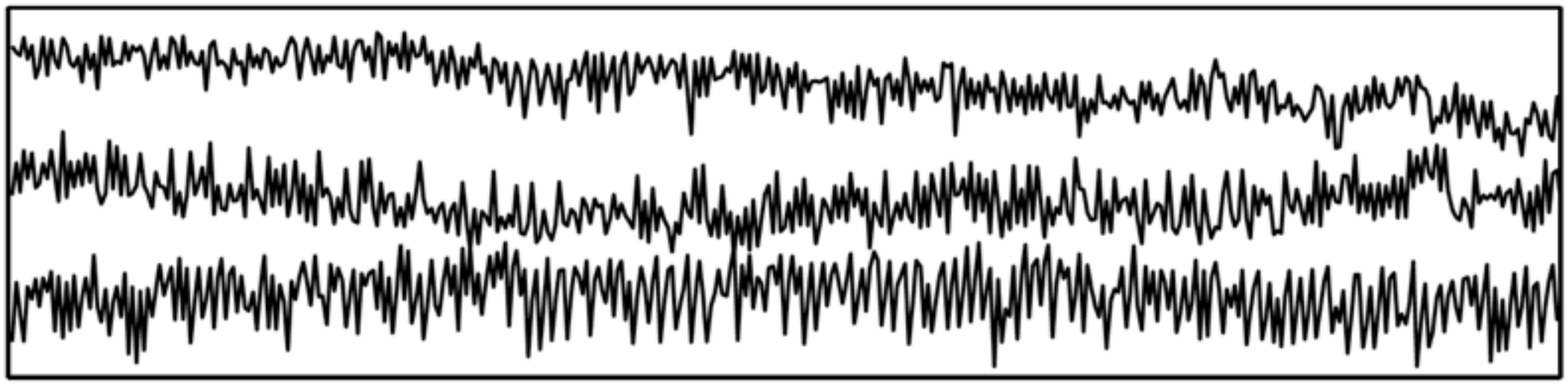
- Noise components
- EPI ‘ghost’ artefacts

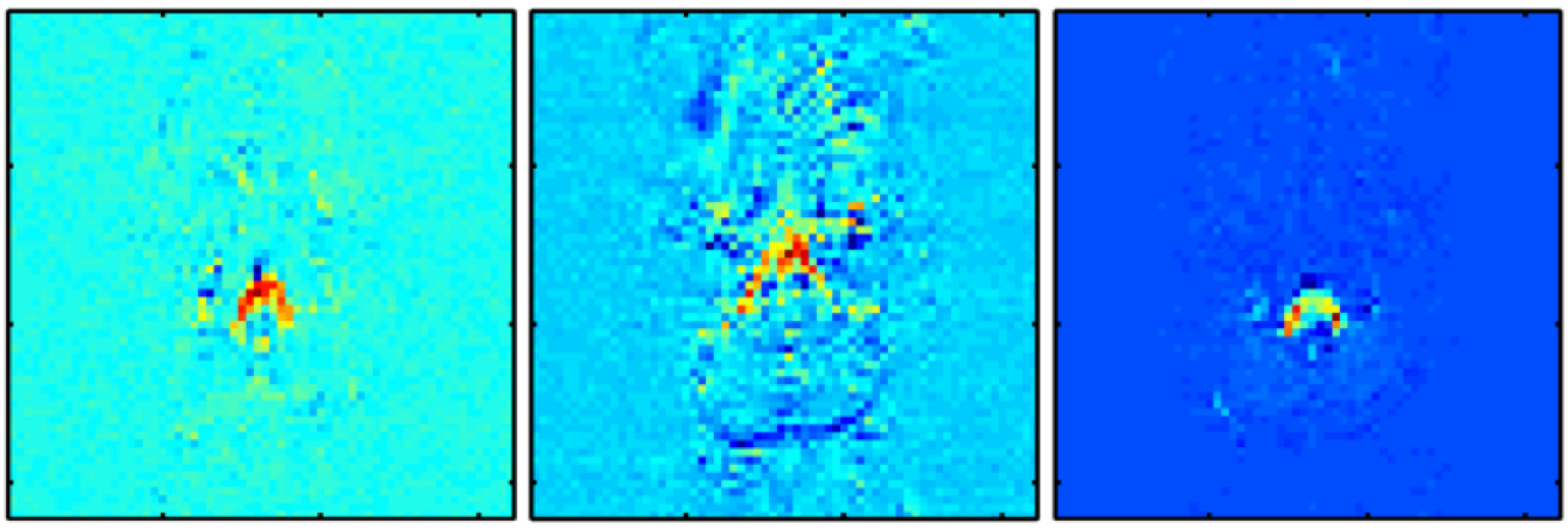


Thanks to C. Beckmann for examples

# Analysis pros & cons +

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

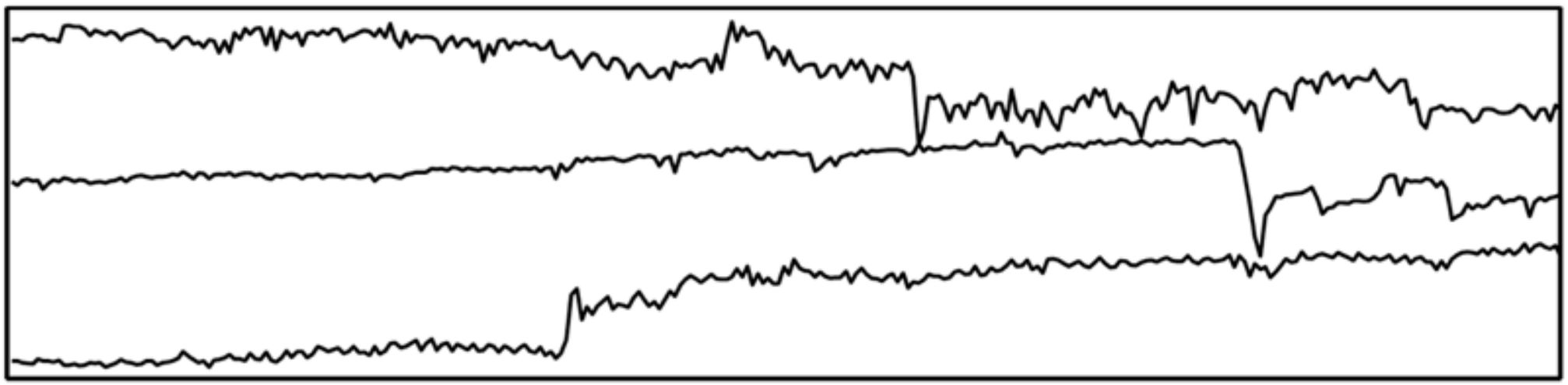


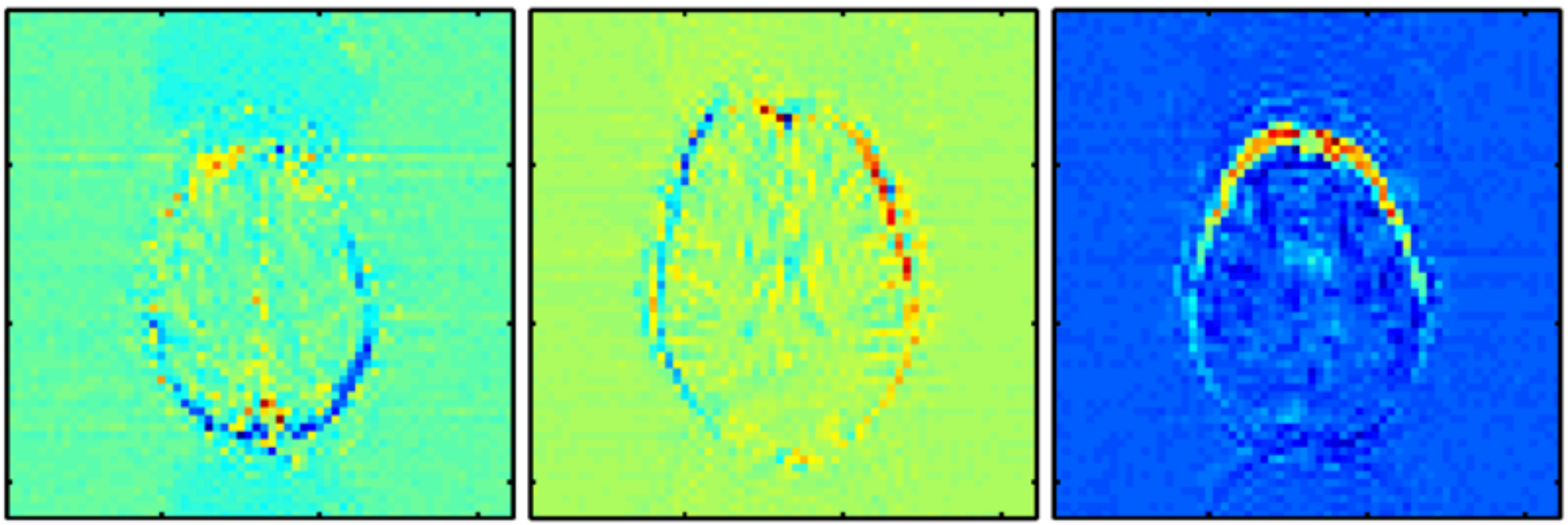


Thanks to C. Beckmann for examples

# Analysis pros & cons +

- Noise components
- Head motion

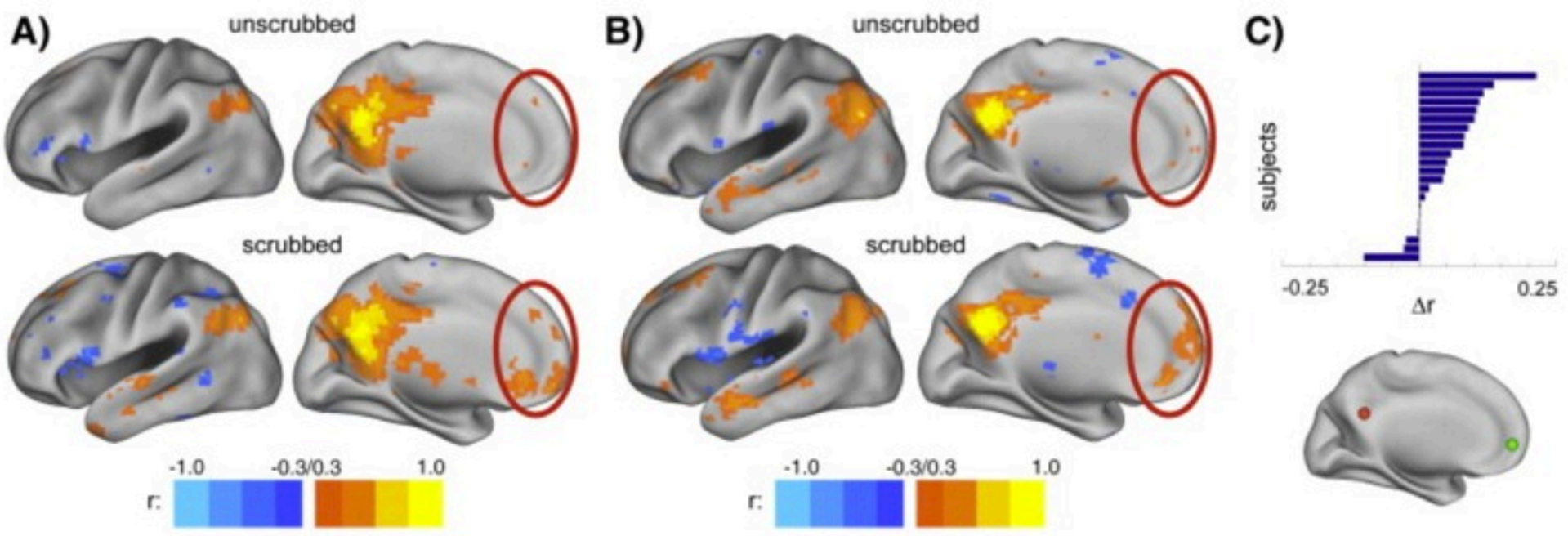




Thanks to C. Beckmann for examples

# Motion aside...

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

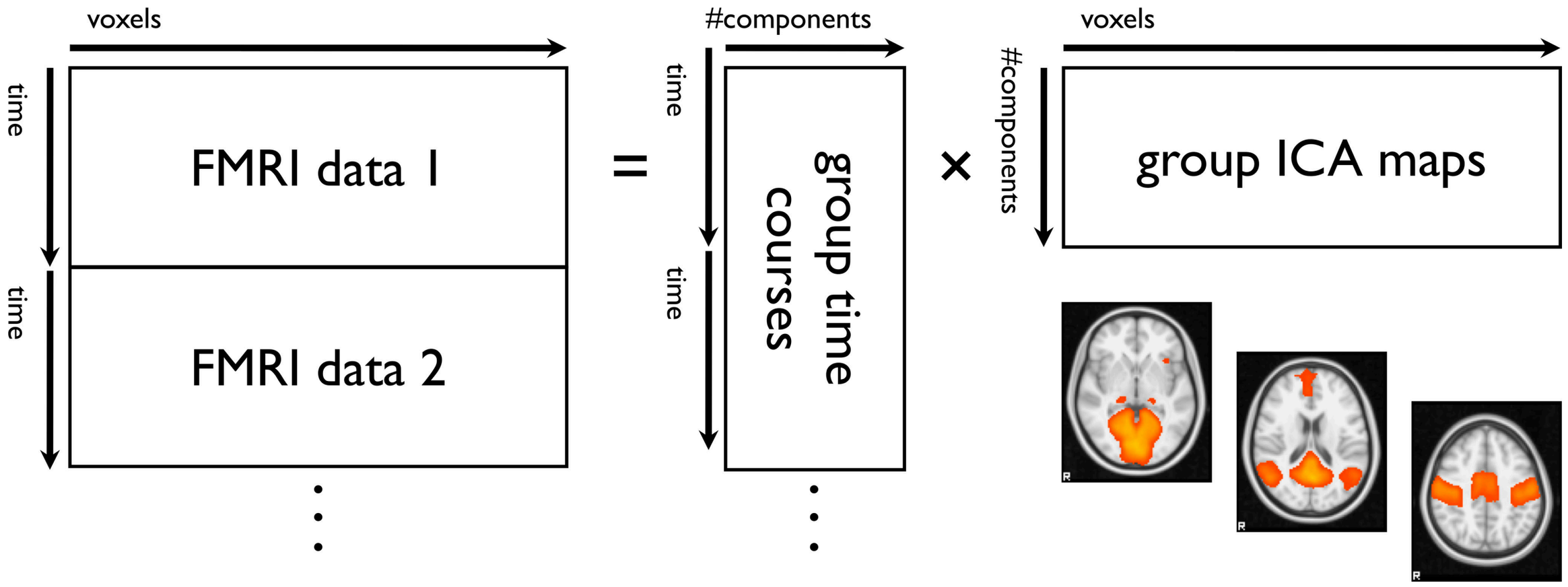



Power et al. (2012)
*NeuroImage*

# 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*

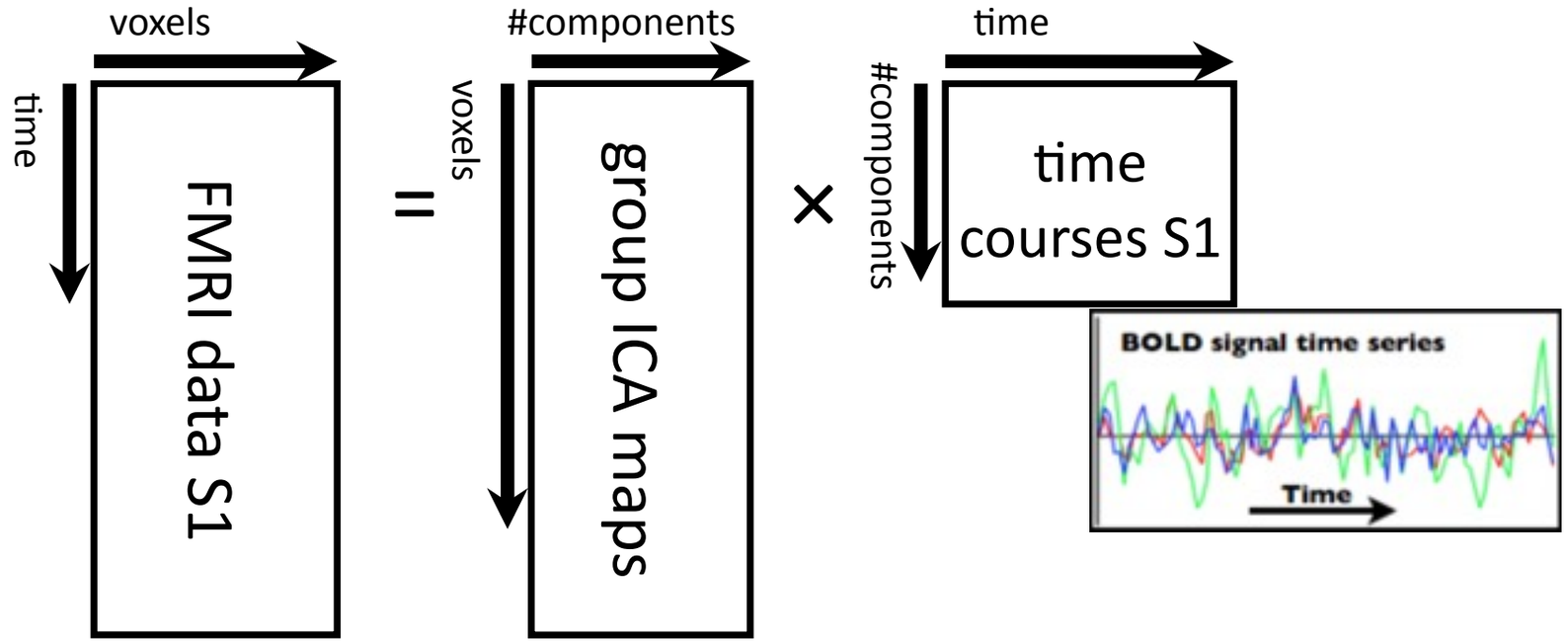
# Multi-session RSN identification: concat-ICA




Calhoun et al. (2001) *HBM*; Beckmann & Smith (2005) *Neuroimage*

# Multi-session RSN *comparison*: dual regression

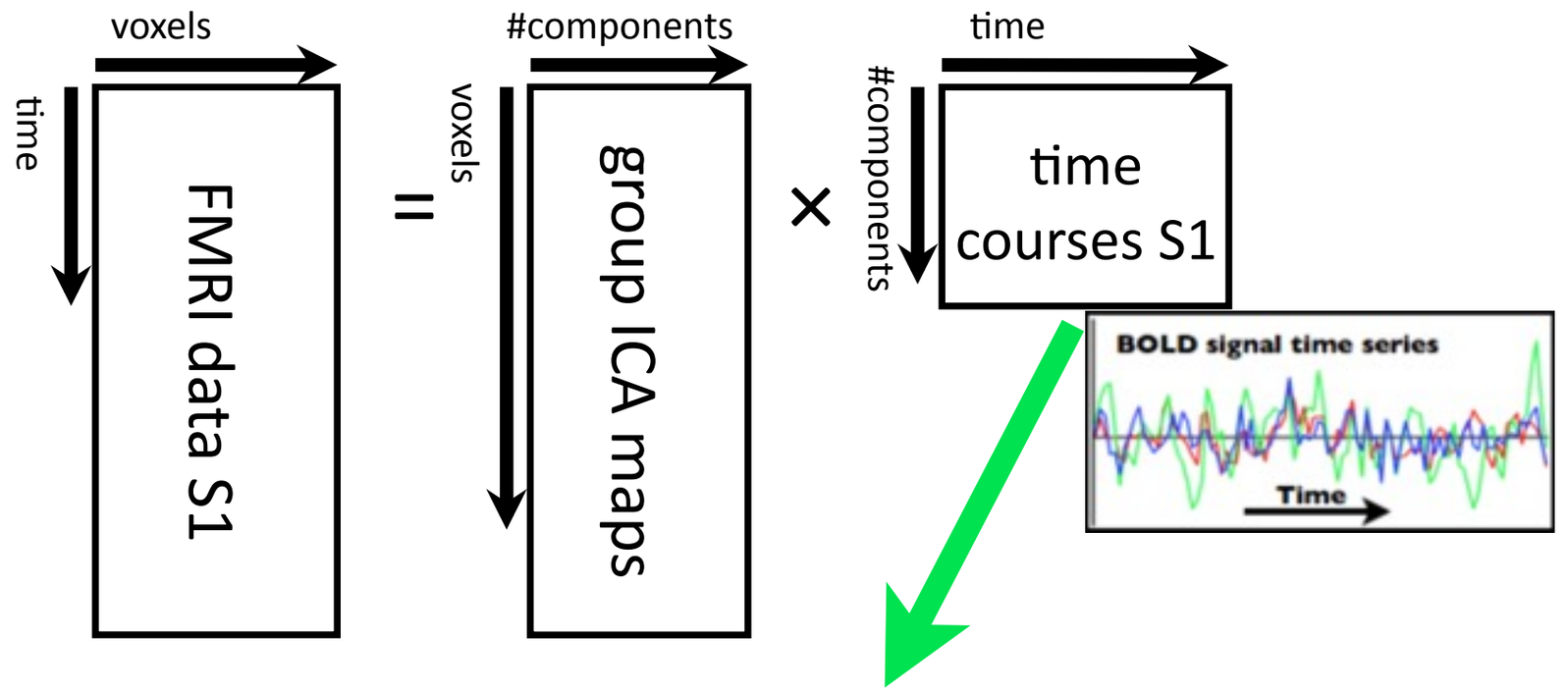
1.



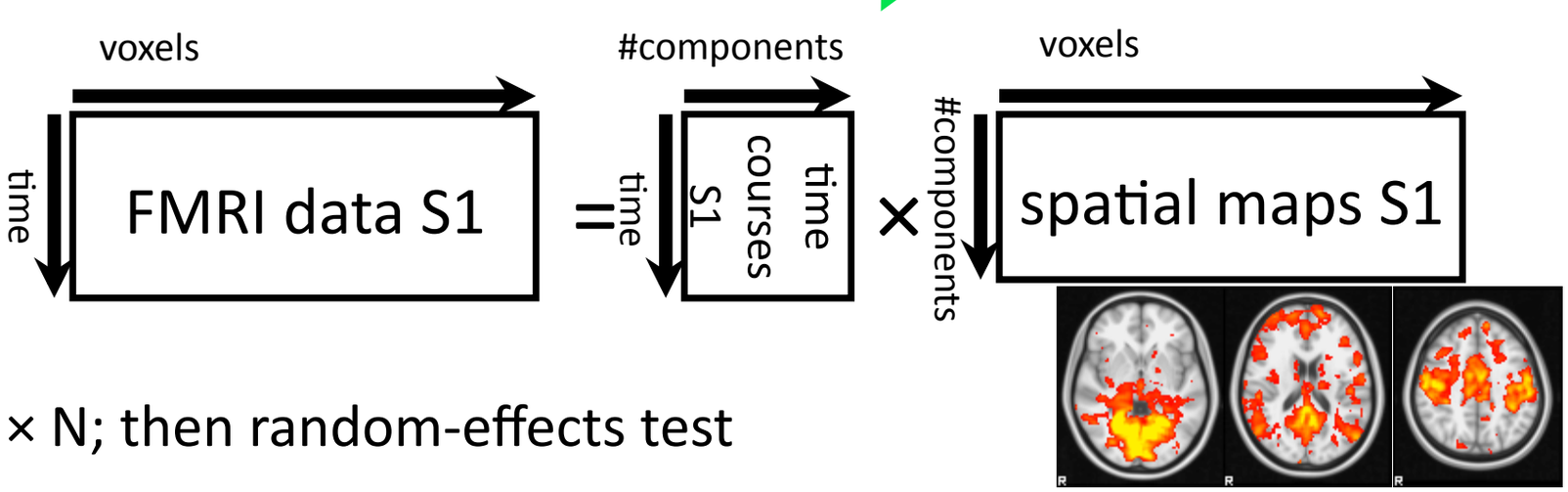

Filippini et al. (2009) *PNAS*; Beckmann et al. (2009) *OHBM [abstr]*

# Multi-session RSN *comparison*: dual regression

1.




2.

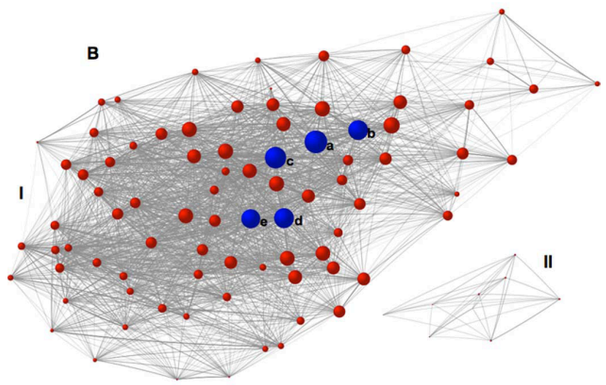



3. Repeat × N; then random-effects test

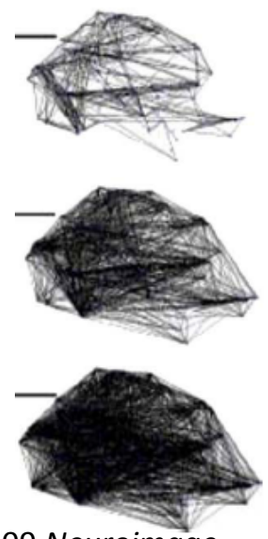
Filippini et al. (2009) *PNAS*; Beckmann et al. (2009) *OHBM [abstr]*

# Alternative methods

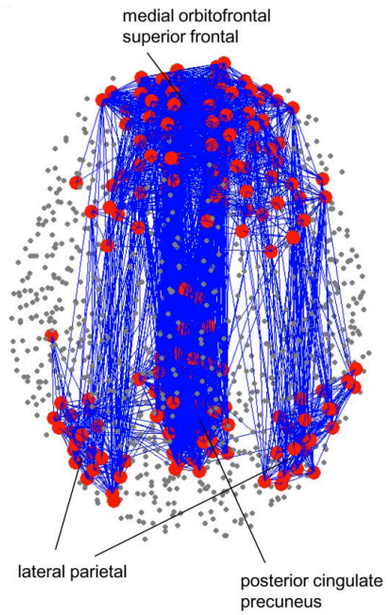
- Graph theoretical approaches
  - ‘Nodes’ & ‘Edges’
  - What’s your cut-off point?
- Amplitude of low-frequency fluctuations (ALFF)
- Regional homogeneity (ReHo)
- Clustering




Buckner et al. ’09 *J Neurosci*



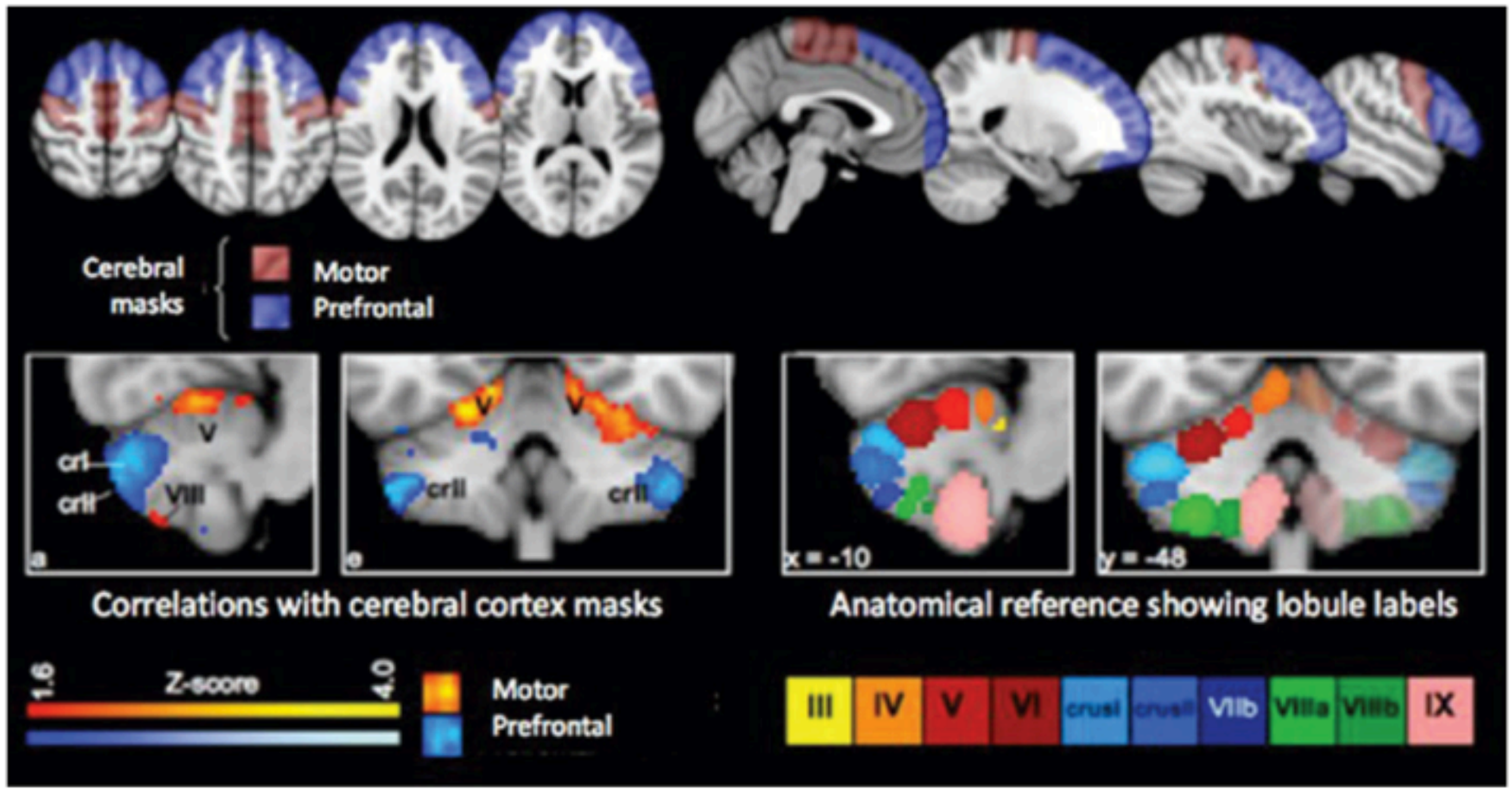
Bullmore et al. ’09 *Neuroimage*




Honey et al. ’09 *PNAS*

# 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

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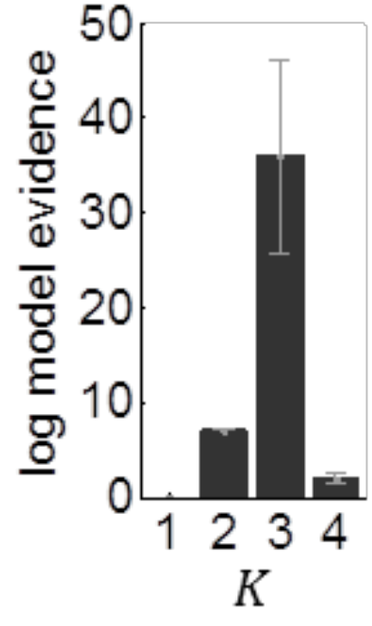
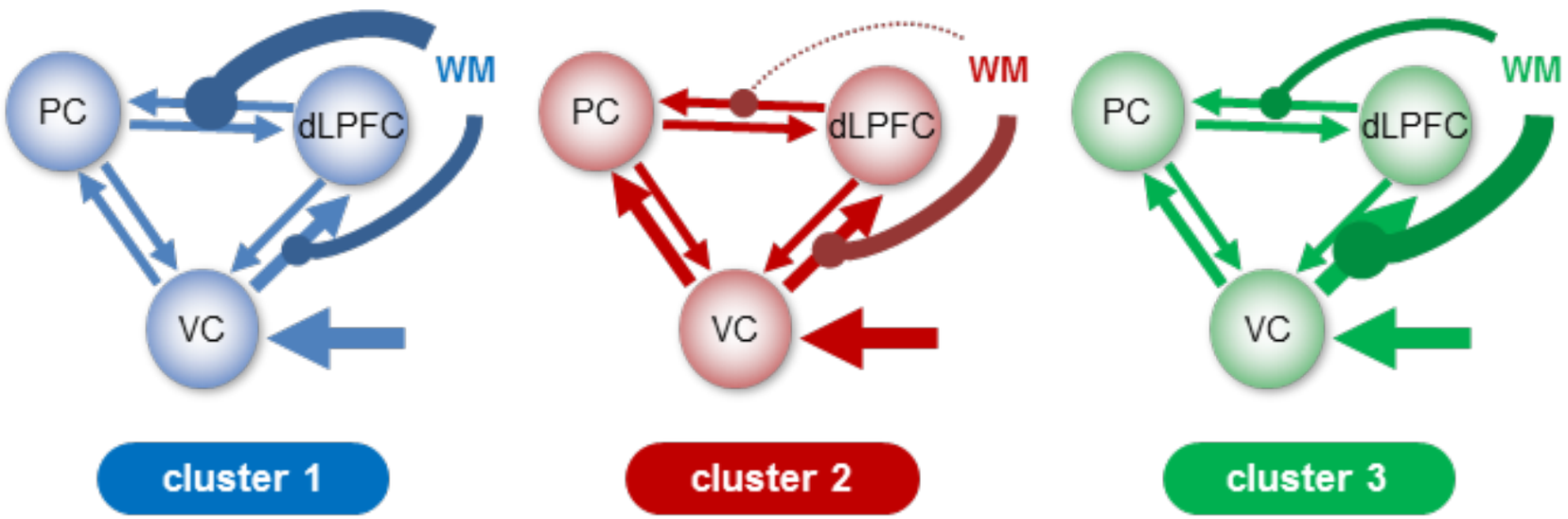
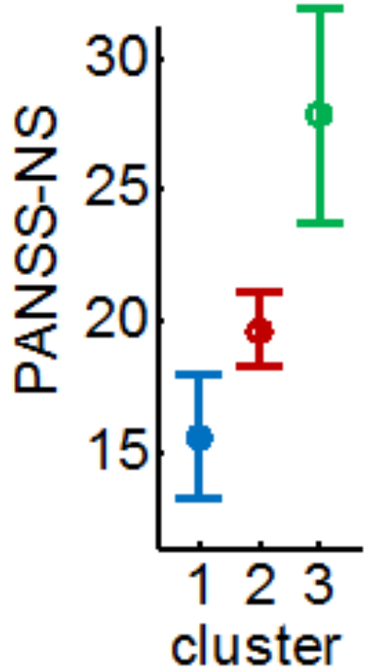
# Detecting subgroups of patients in schizophrenia

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

**Optimal cluster solution**



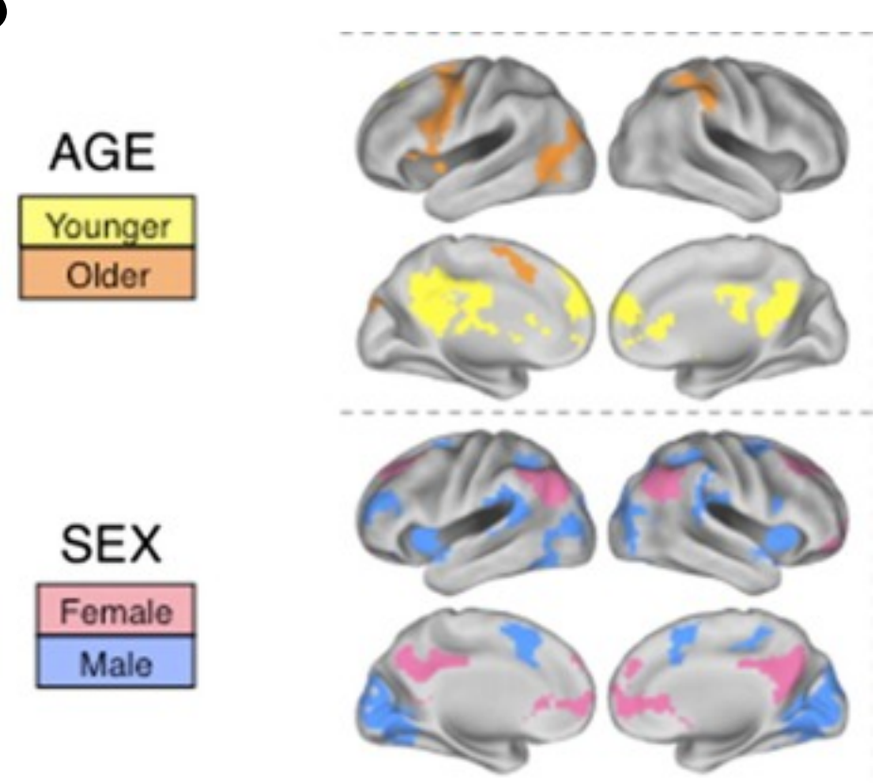




Brodersen et al (2014) *Neuroimage: Clinical*

# 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

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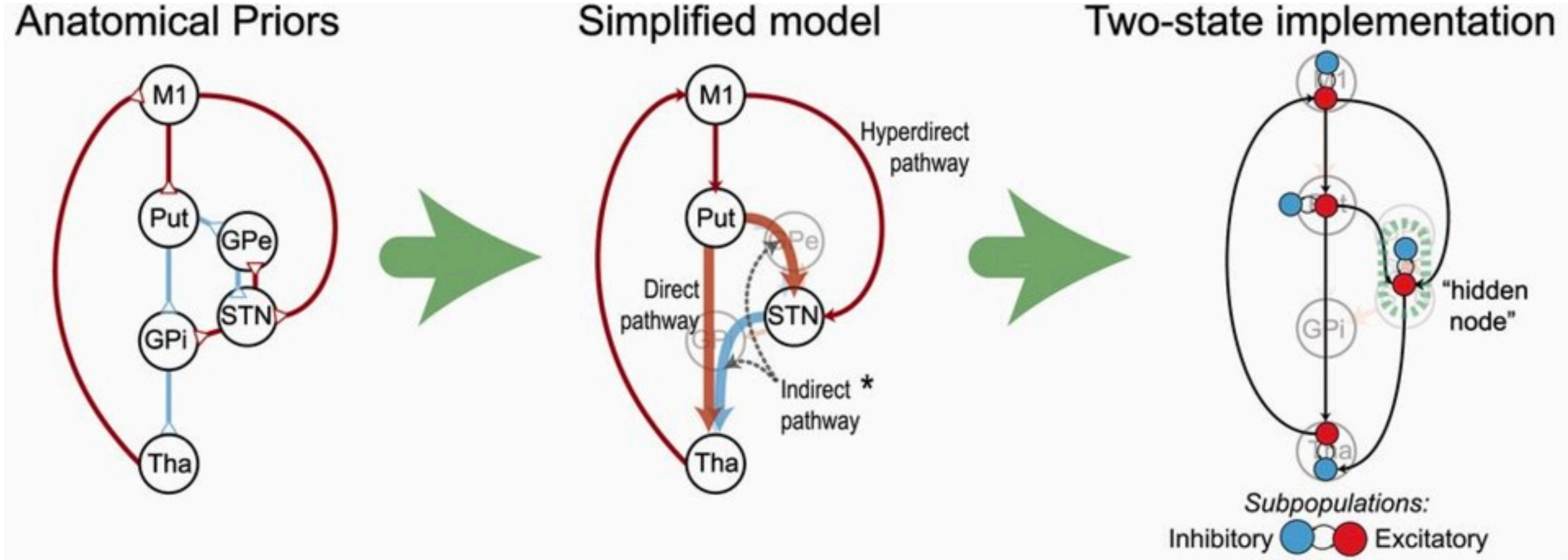
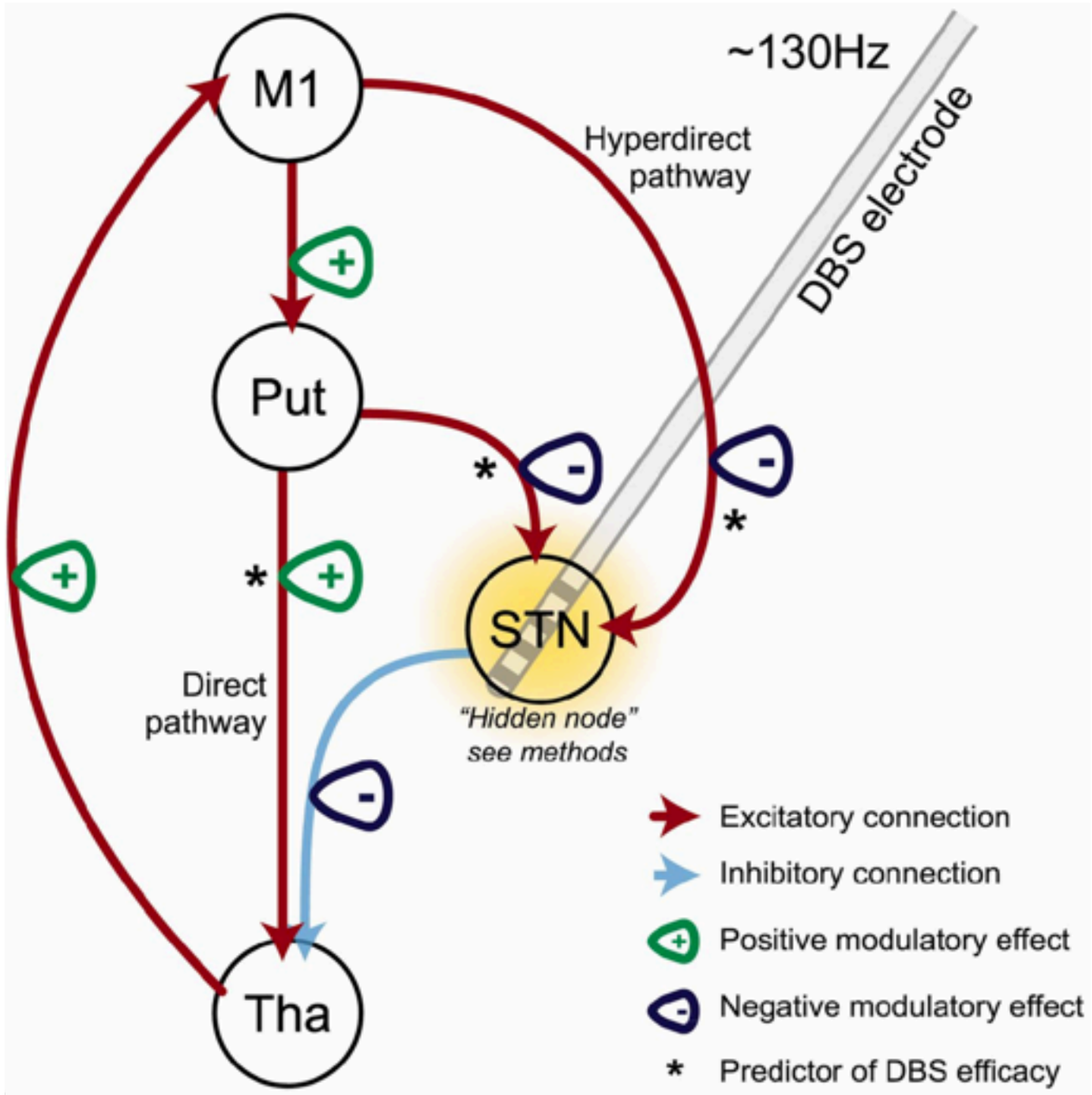
# ‘Mechanistic’ analysis of resting-state fMRI data




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


- Buckner, Krienen & Yeo (2013) Opportunities and limitations of intrinsic functional connectivity MRI. *Nat Neurosci* 16:832-837

- Cole, Smith & Beckmann (2010) Advances and pitfalls in the analysis and interpretation of resting-state fMRI data. *Frontiers in Systems Neuroscience* 4:8

- Fox & Greicius (2010) Clinical applications of resting state functional connectivity. *Front Syst Neurosci* 4:19

- Margulies et al. (2010) Resting developments: a review of fMRI post-processing strategies for spontaneous brain activity. *MAGMA* 23:289-307

- Murphy, Birn & Bandettini (2013) Resting-state fMRI confounds and cleanup. *NeuroImage* 80:349-359

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