ETH zürich University of Zurich[UZH]

"Resting-state" fMRI

SPM Course Zürich, 17-Feb-2016

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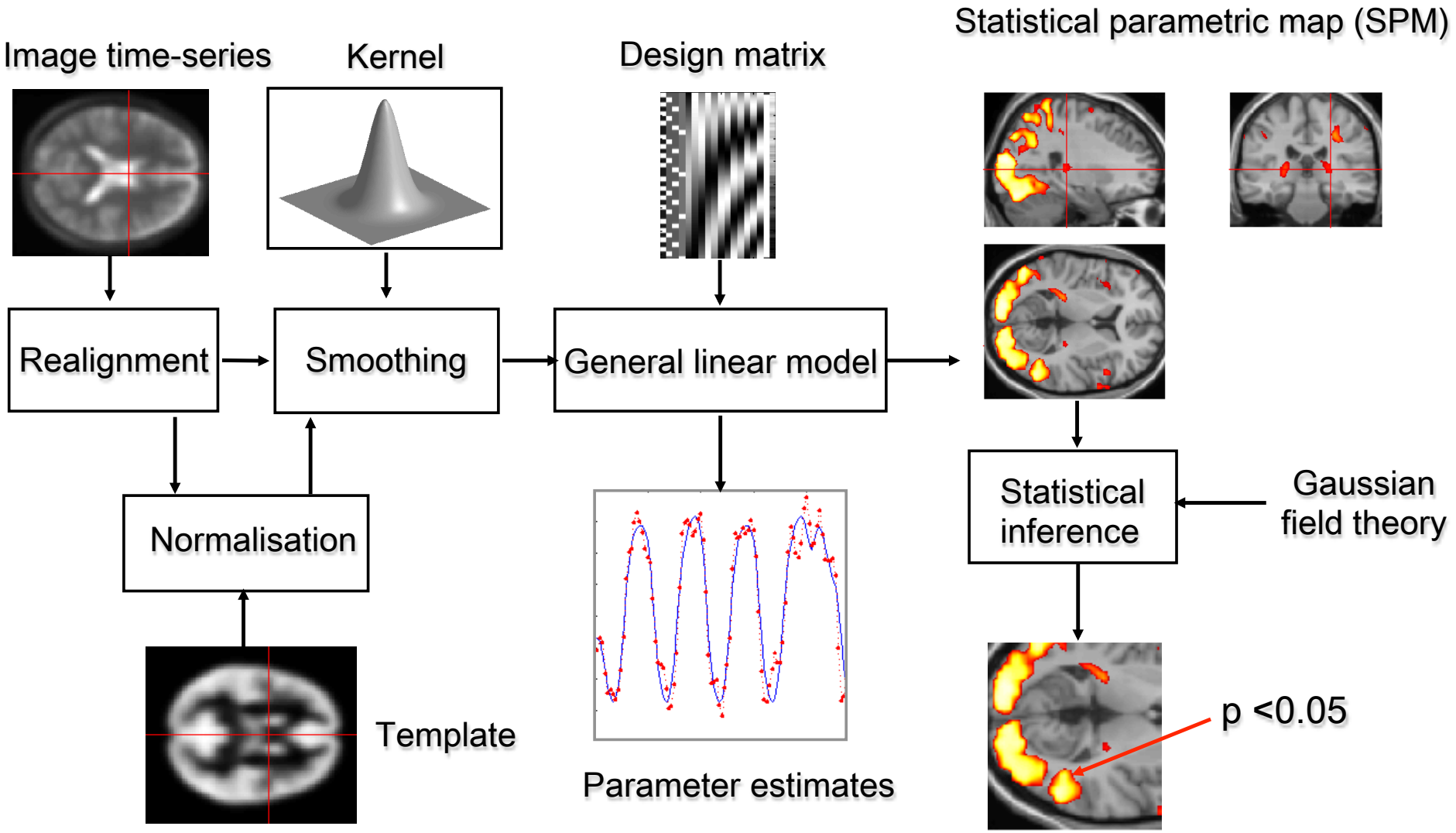
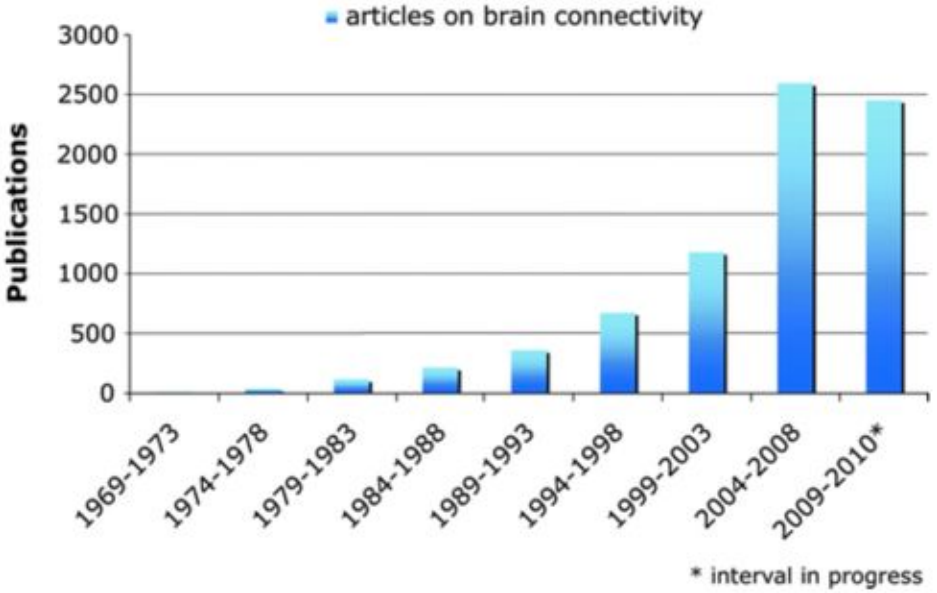
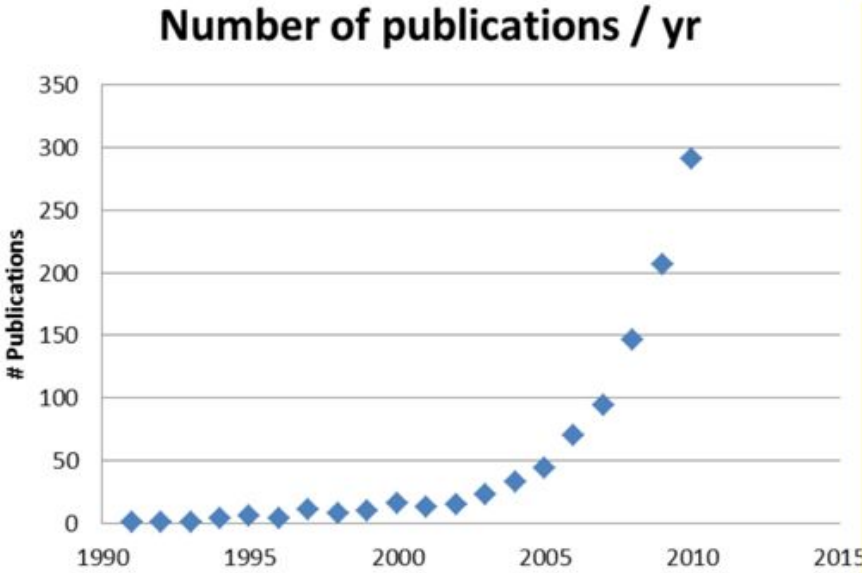
Overview of SPM – Resting state fMRI



‘Exponential’ interest



Pawela & Biswal (2011) *Brain Connectivity*

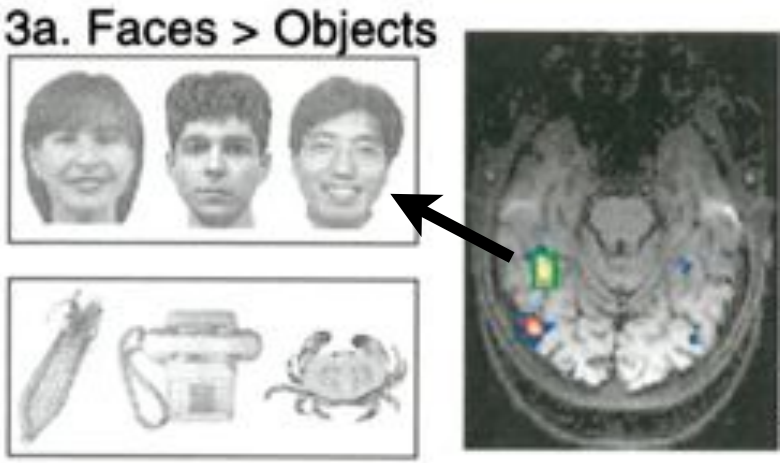


Scopus search: (“functional Magnetic Resonance Imaging” OR “functional MRI” OR “fMRI”) AND (((rest OR resting) AND connectivity) OR “resting state” OR “spontaneous fluctuations” OR “intrinsic fluctuations”)

Birn (2012) *NeuroImage*

Paradigm shift

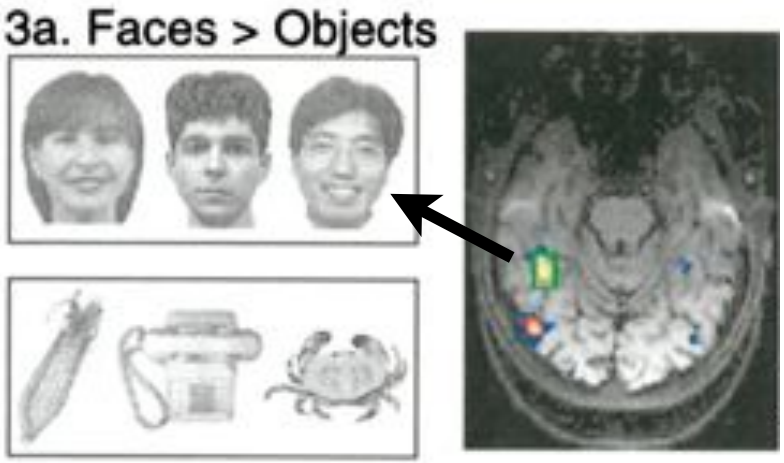
- Functionality: Local ⟶ Distributed



Kanwisher et al. (1997)
J Neurosci

Paradigm shift

- Functionality: Local ⟶ Distributed



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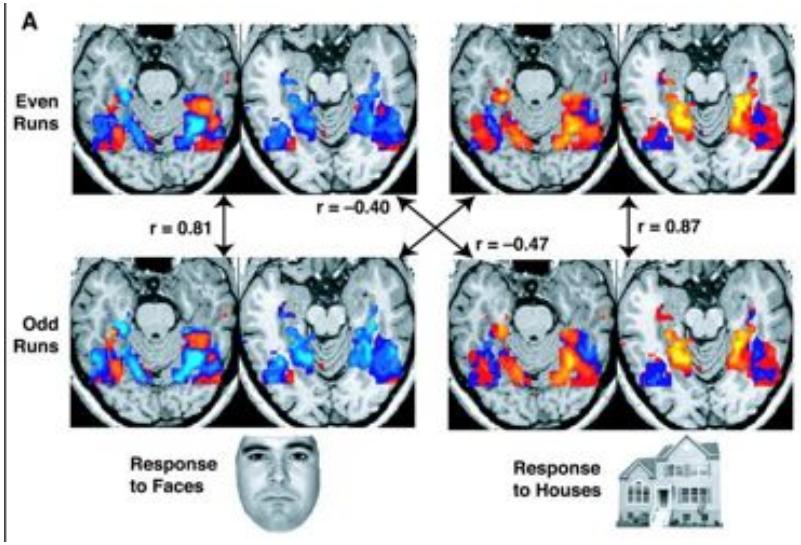
J Neurosci



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

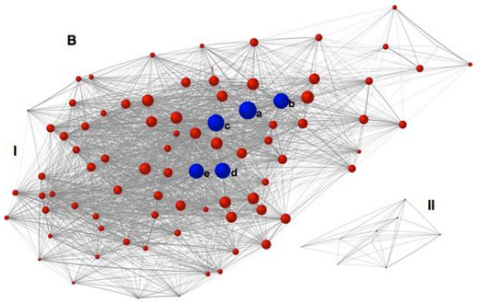
Connectivity

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

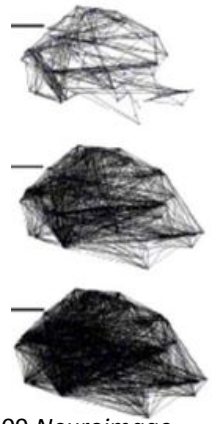
(... also the *Human Connectome Project*, NIH)

Functional connectivity (FC)

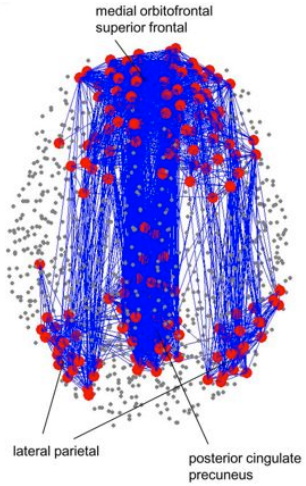
- "Temporal correlations between remote neurophysiological events" - Friston (1994), *HBM*



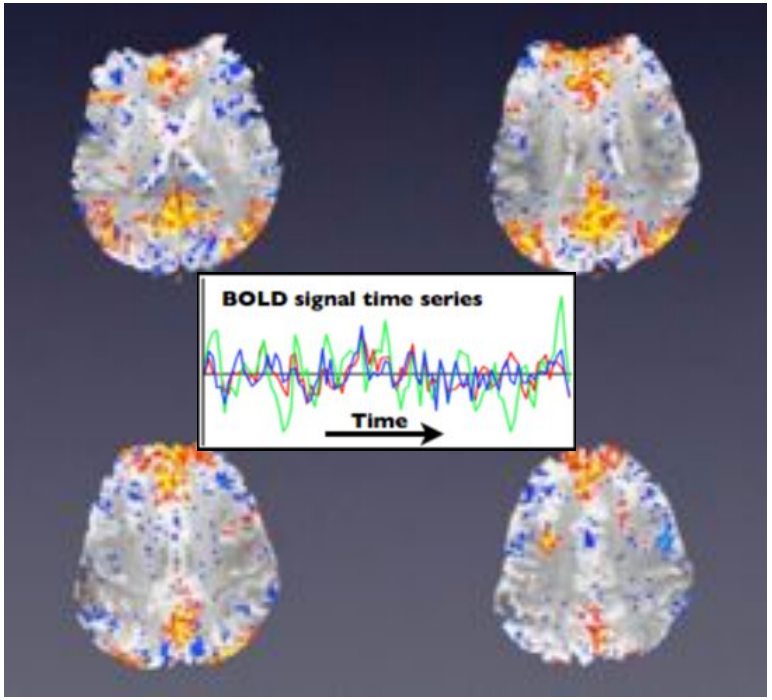
Buckner et al. '09 *J Neurosci*



Bullmore et al. '09 *Neuroimage*

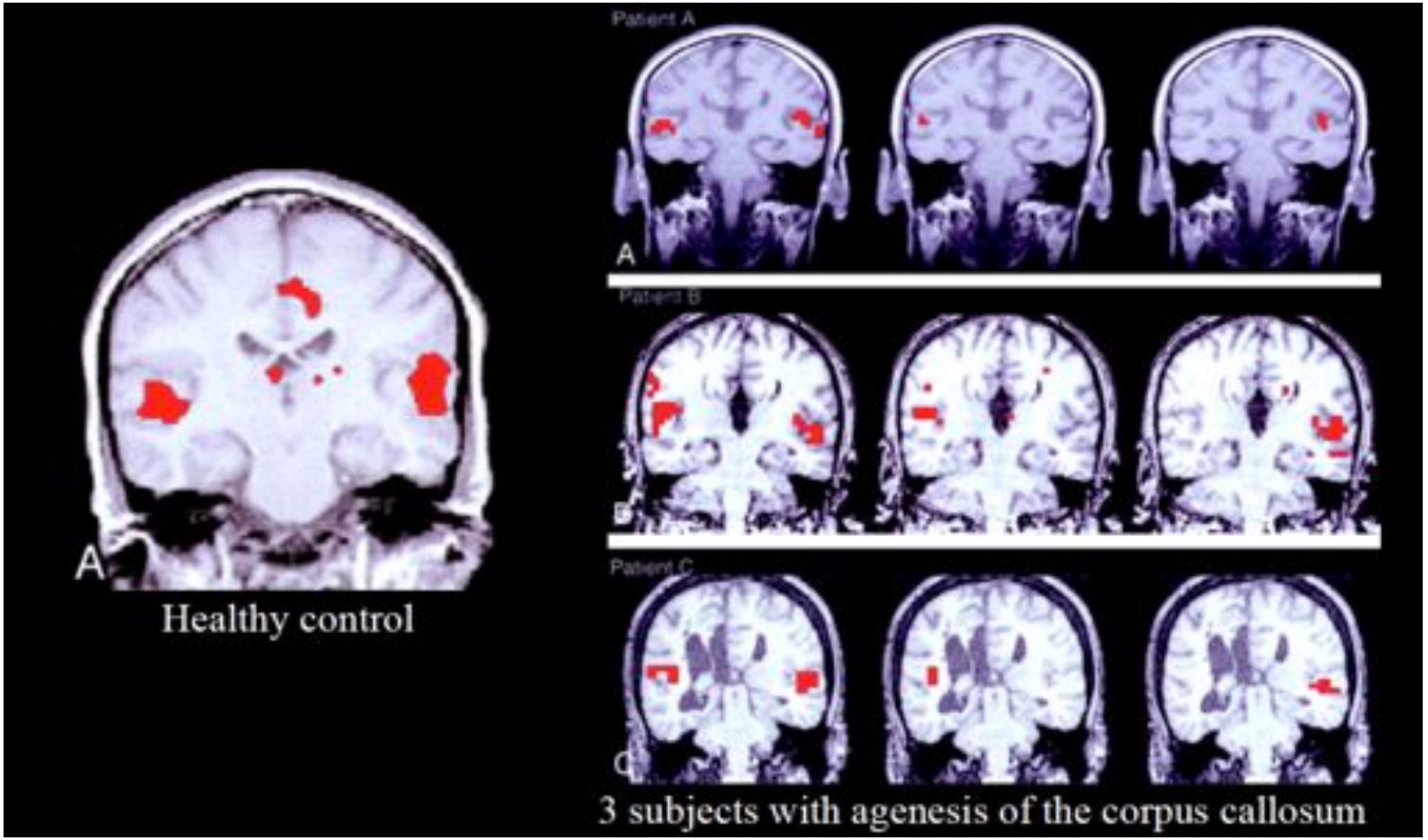


Honey et al. '09 *PNAS*



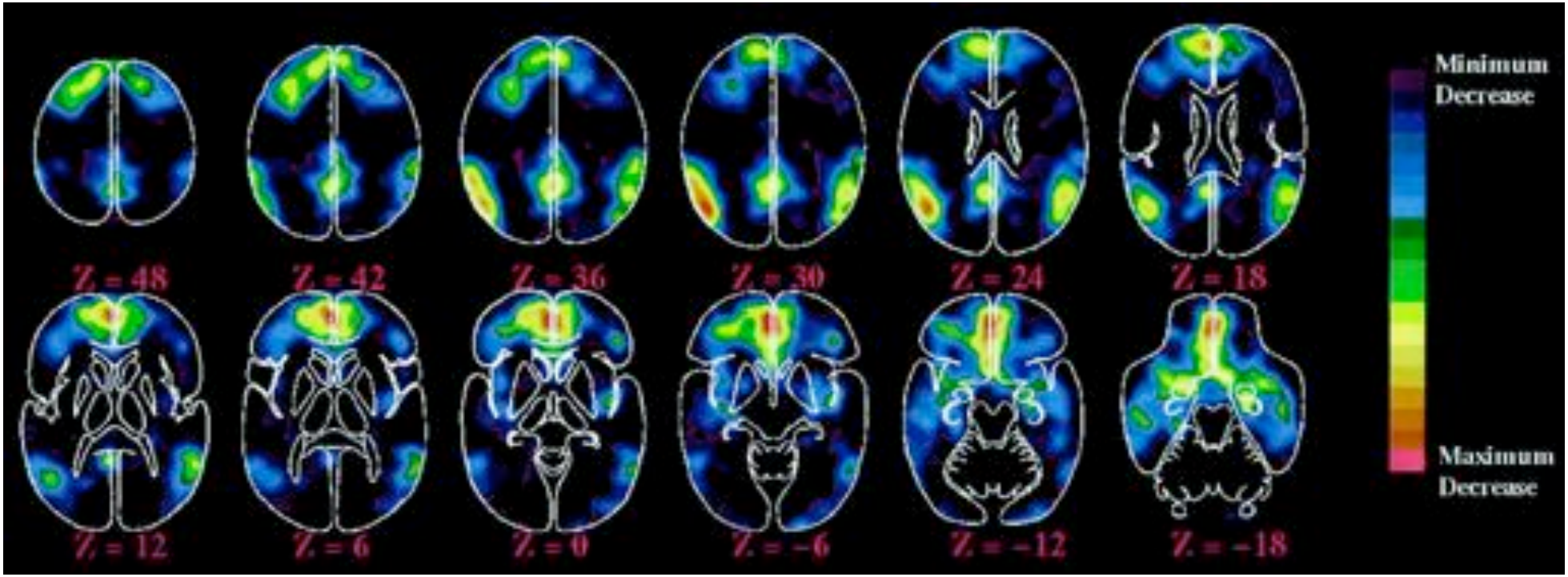
- Large-scale networks

Connectivity: structural = functional?



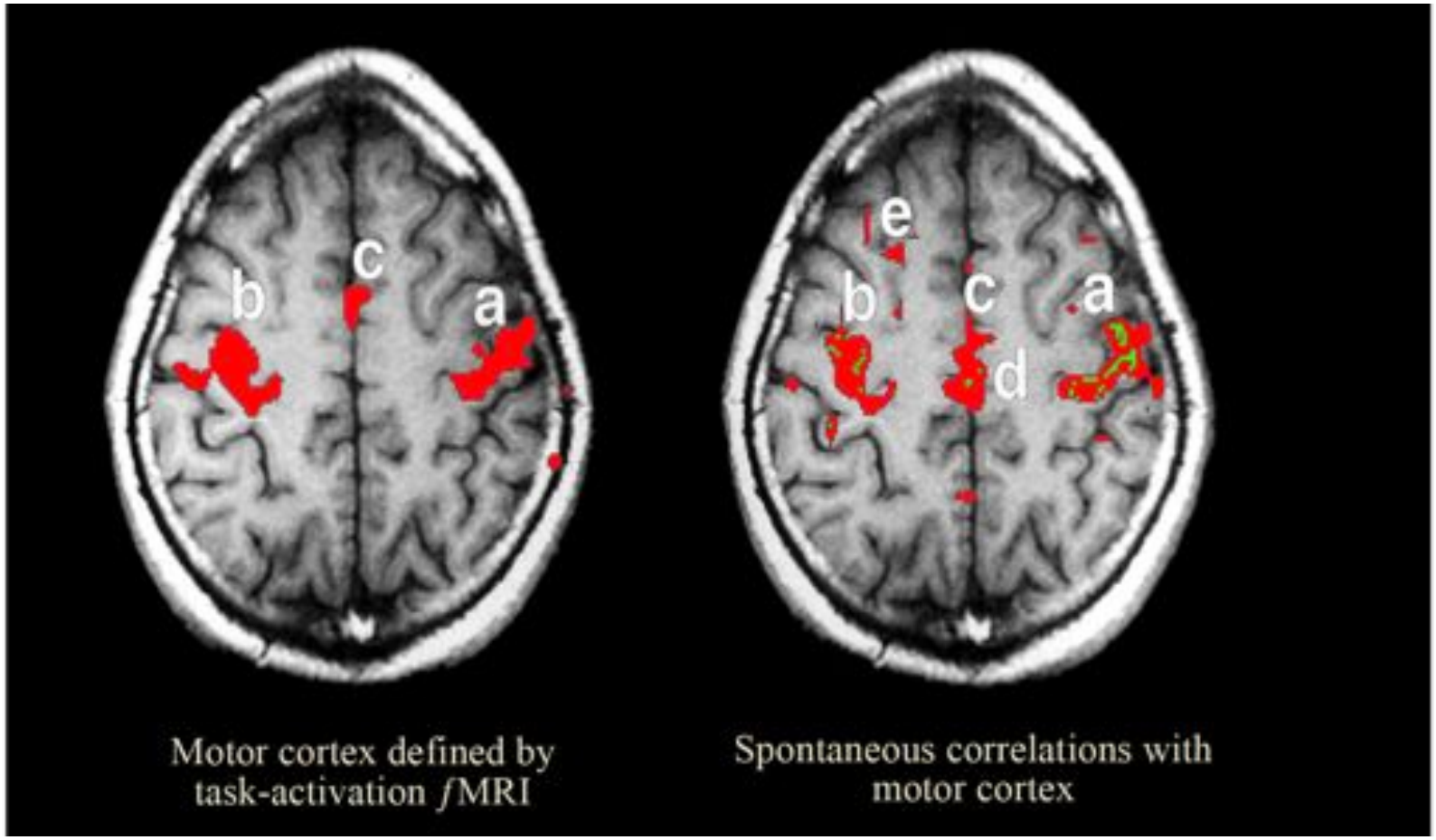
Quigley et al. (2003) *AJNR*

These aren't the blobs you're looking for...



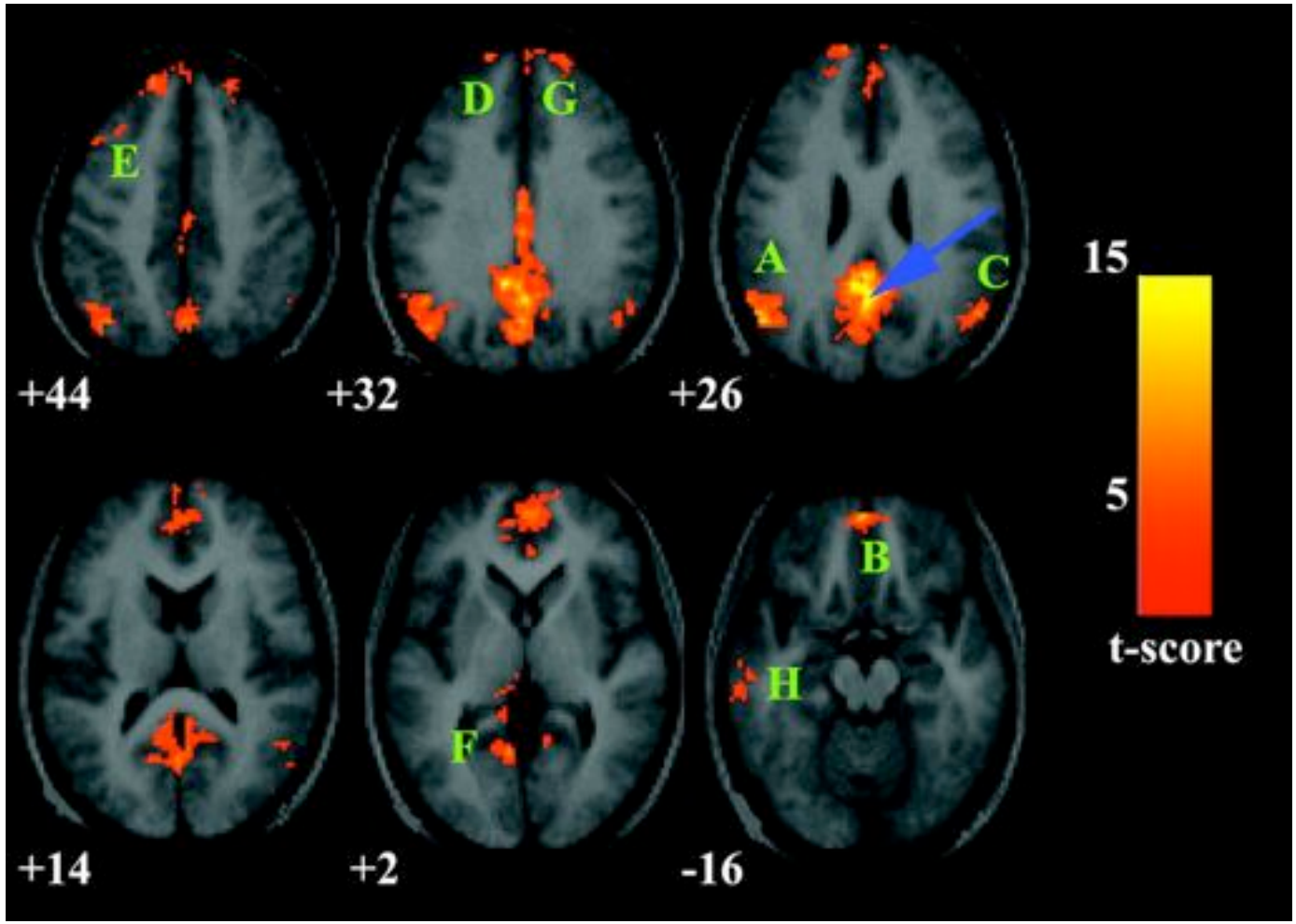
Shulman et al. (1997) *J Cogn Neurosci*; Raichle et al. (2001) *PNAS*

Resting-state FC



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

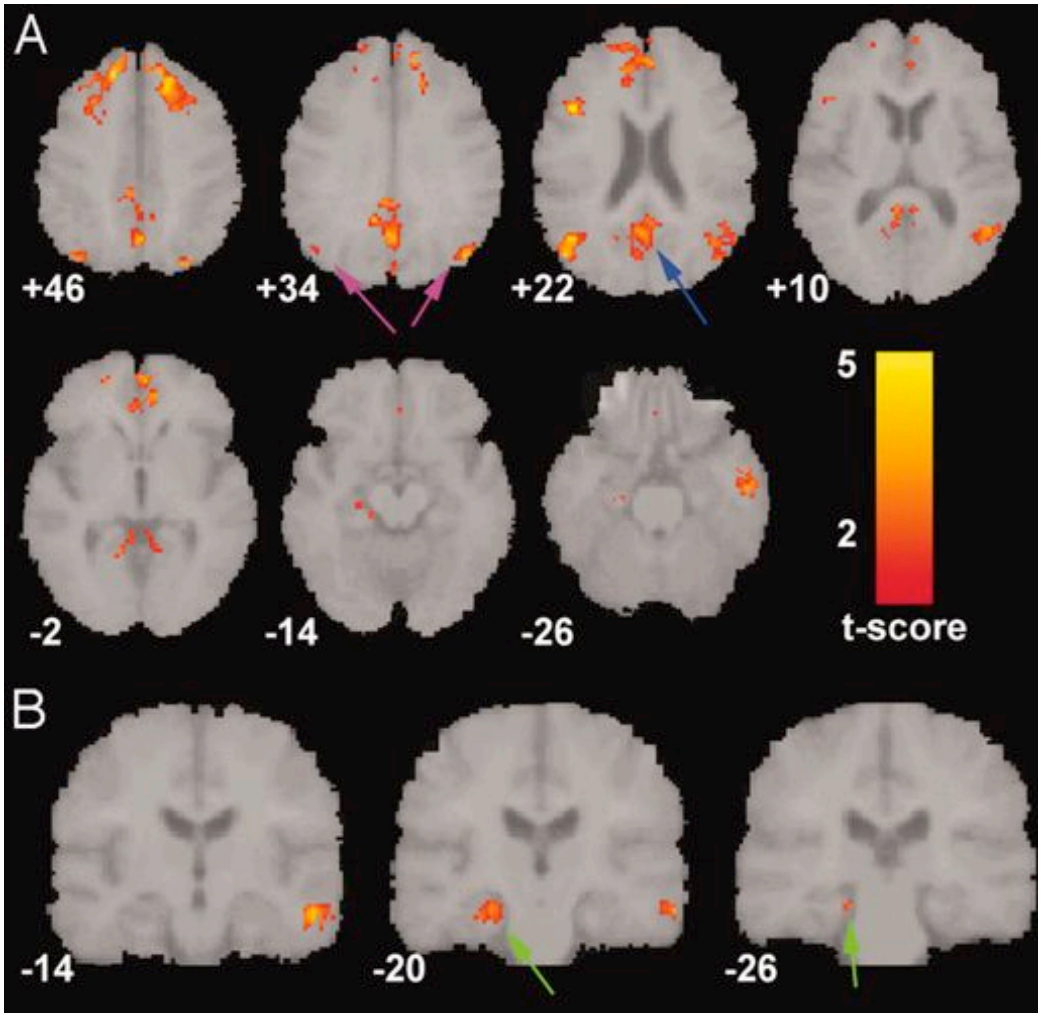
Non-motor networks?



Greicius et al. (2003) *PNAS*

Diseased networks?

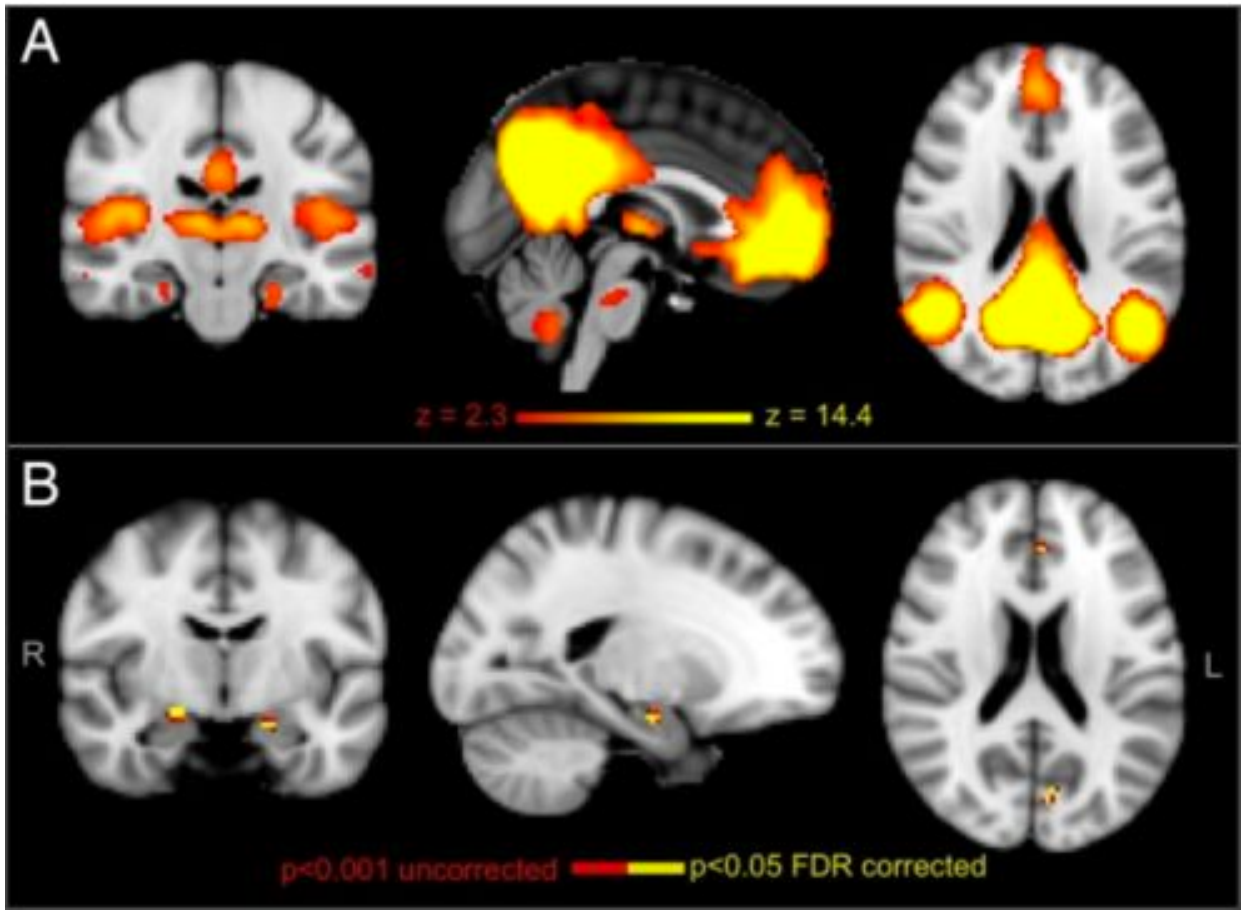
Healthy elderly > Alzheimer's



Greicius et al. (2004) *PNAS*

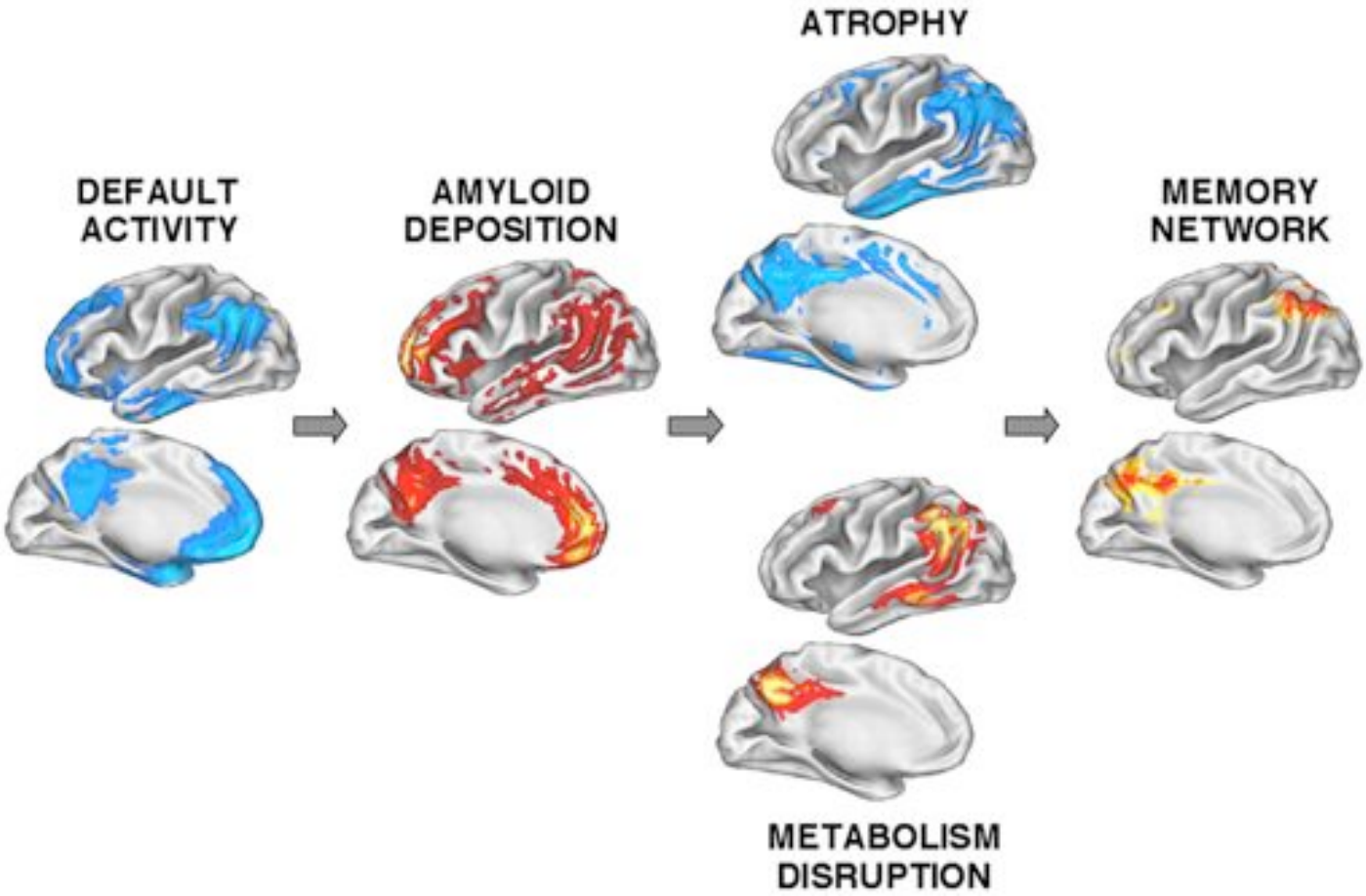
Diseased networks?

Healthy, young, AD predisposed > non-predisposed



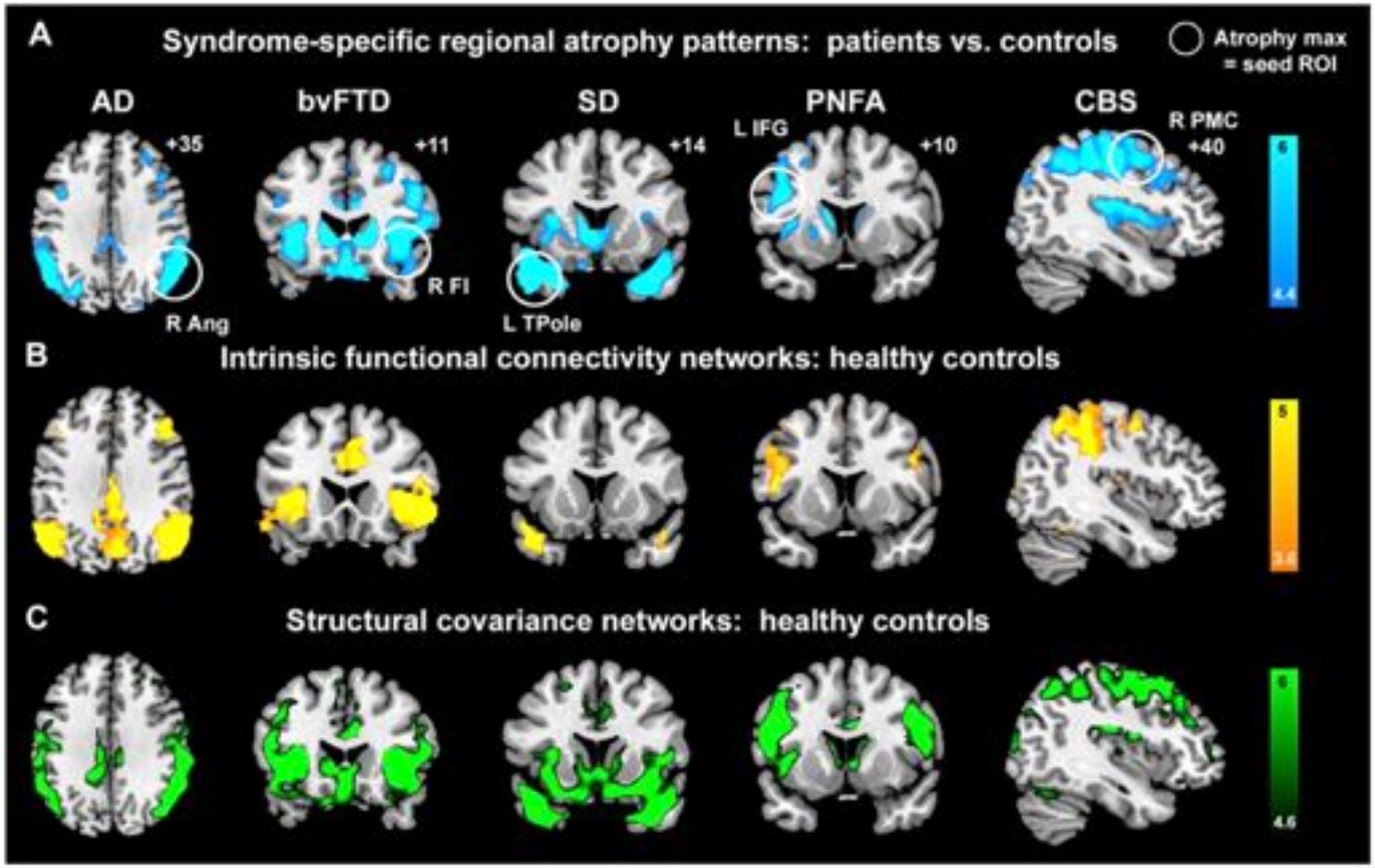
Filippini et al. (2009) *PNAS*

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?

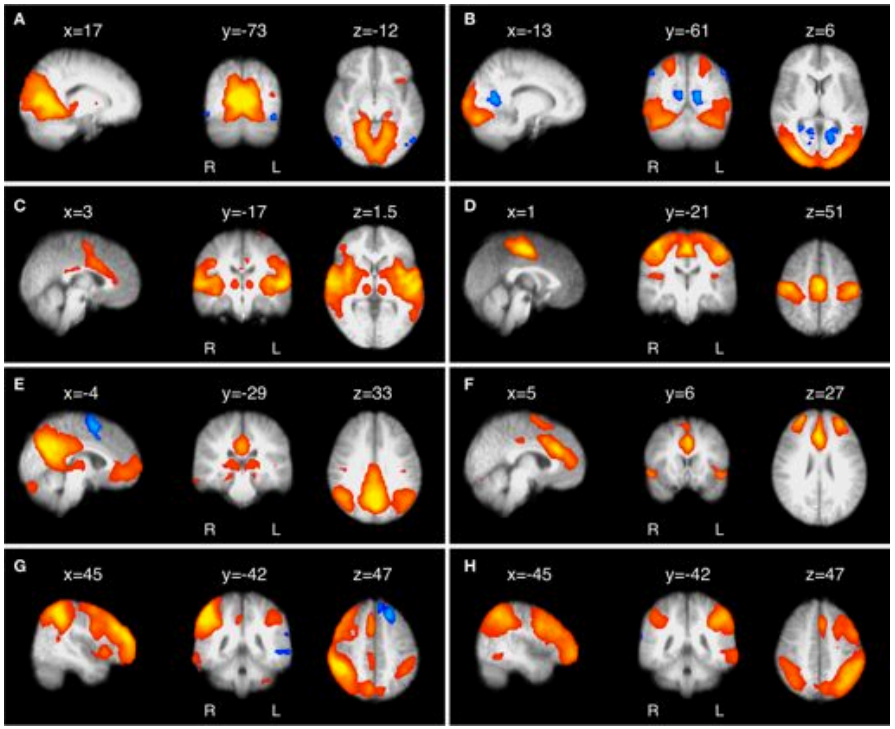
- A note on nomenclature...

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

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

Resting-state networks (RSNs)

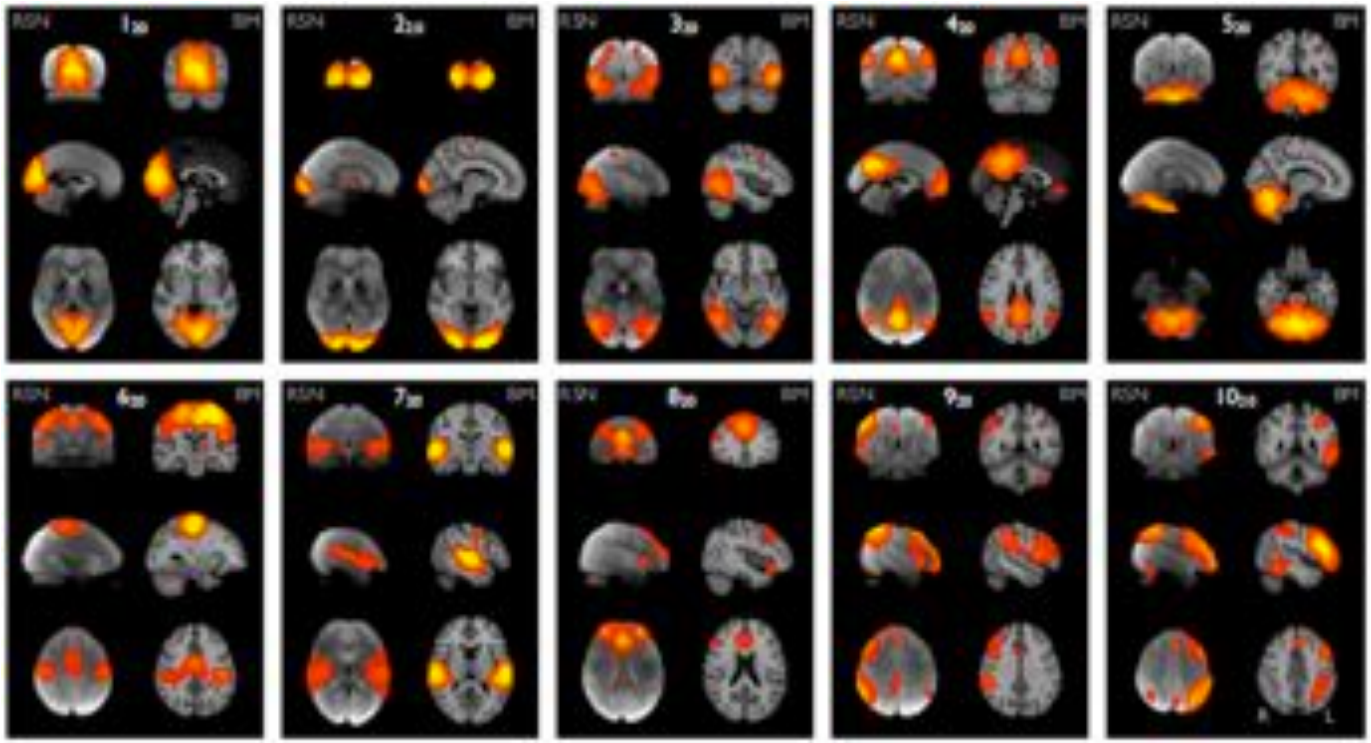
- Multiple spatial patterns of temporally correlated activity



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

Resting-state networks (RSNs)

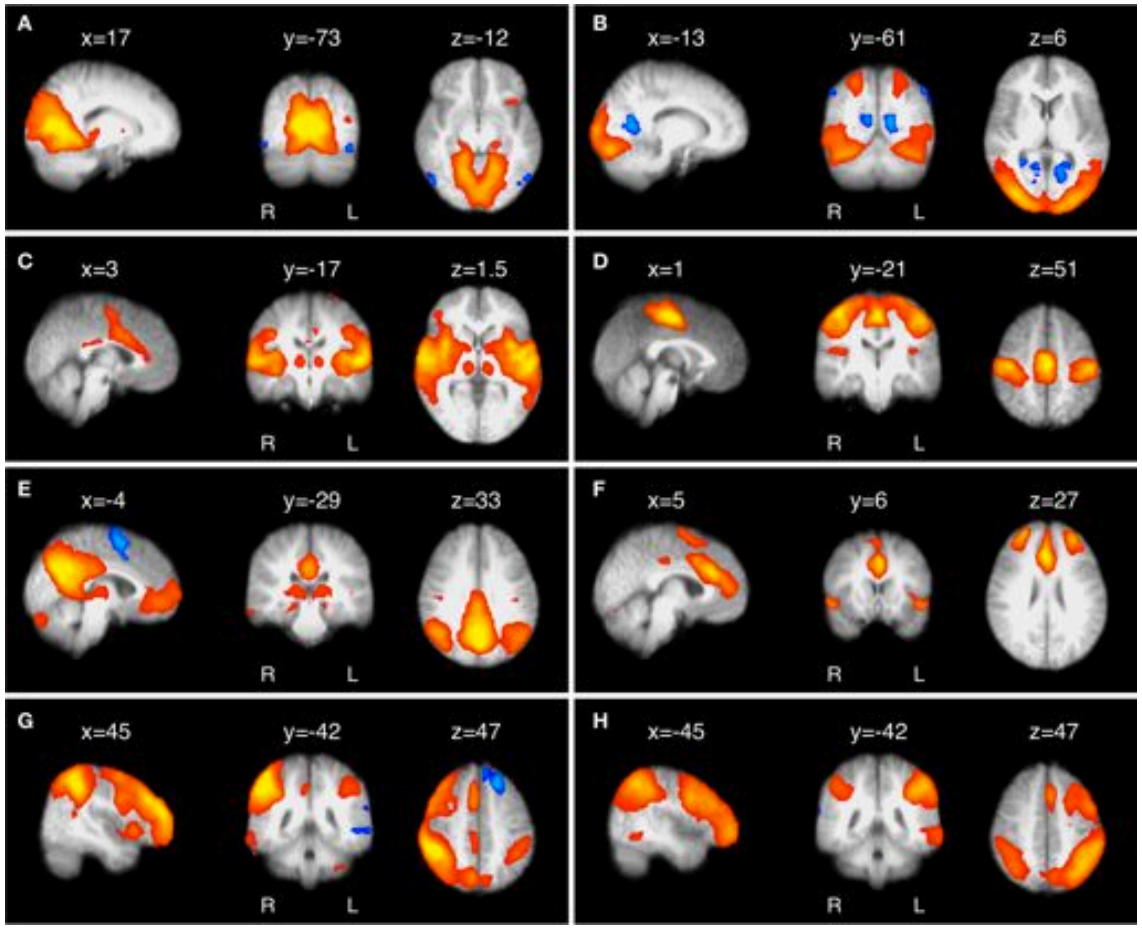
- Multiple spatial patterns of temporally correlated activity
- RSNs reflect distinct, large-scale neuronal functional systems
- Can be identified in absence of strictly-defined models



Smith et al. (2009)
PNAS

Resting-state networks (RSNs)

- Spatial characteristics: (dys)function?



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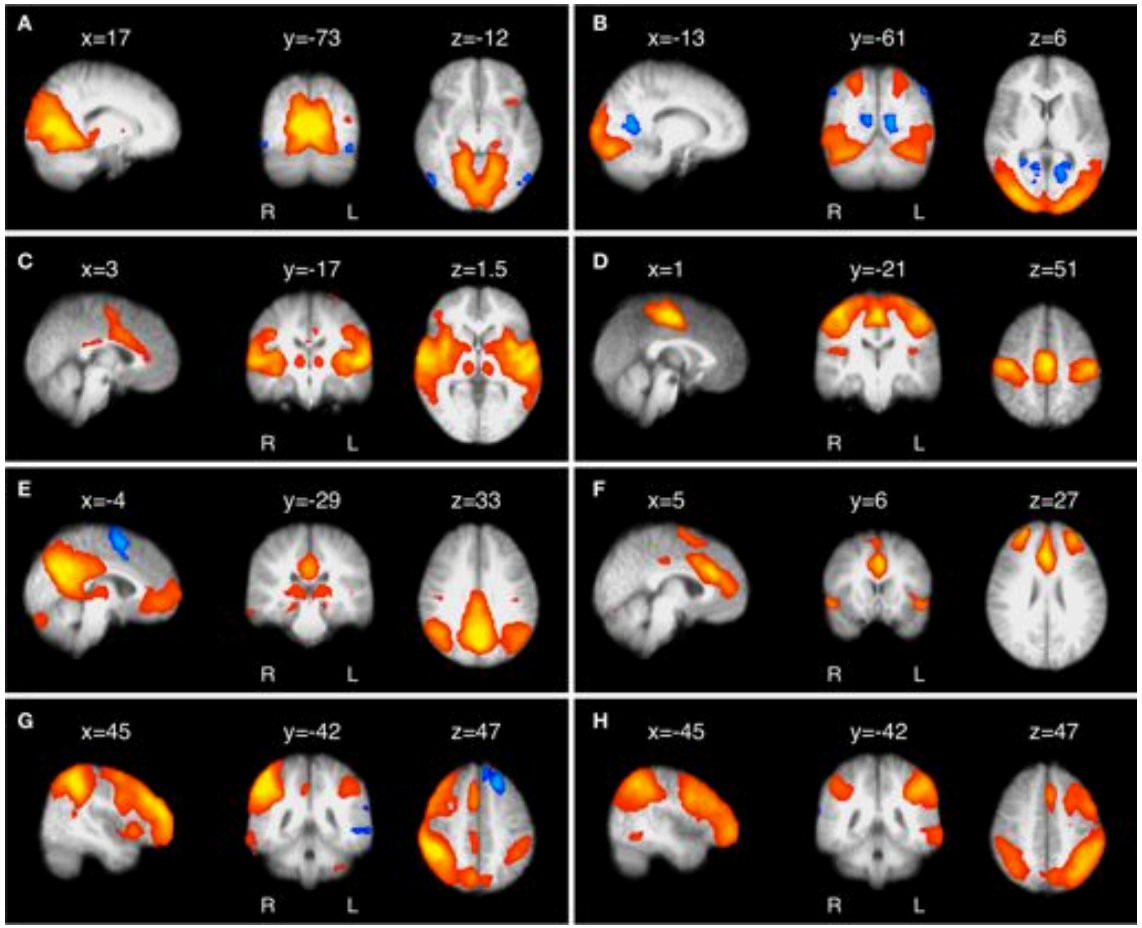
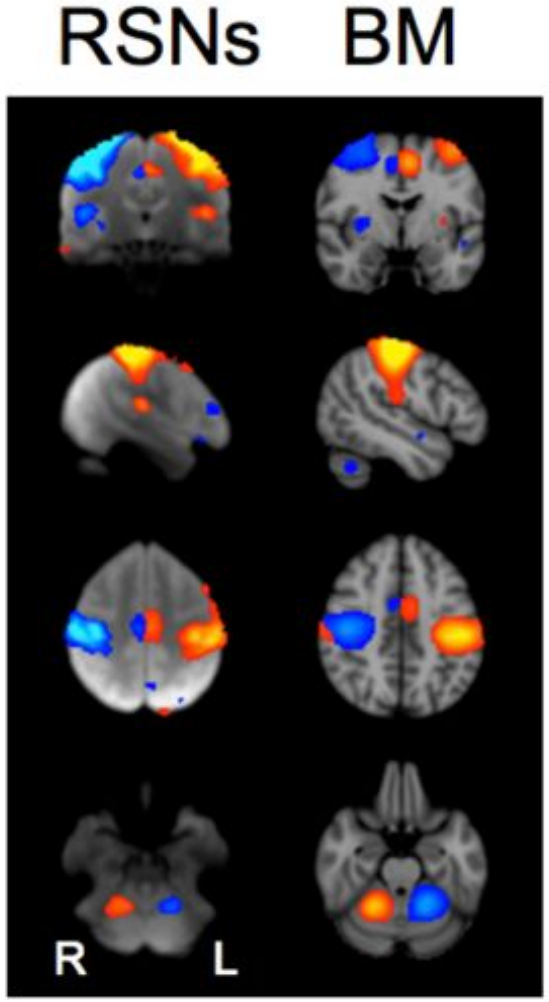
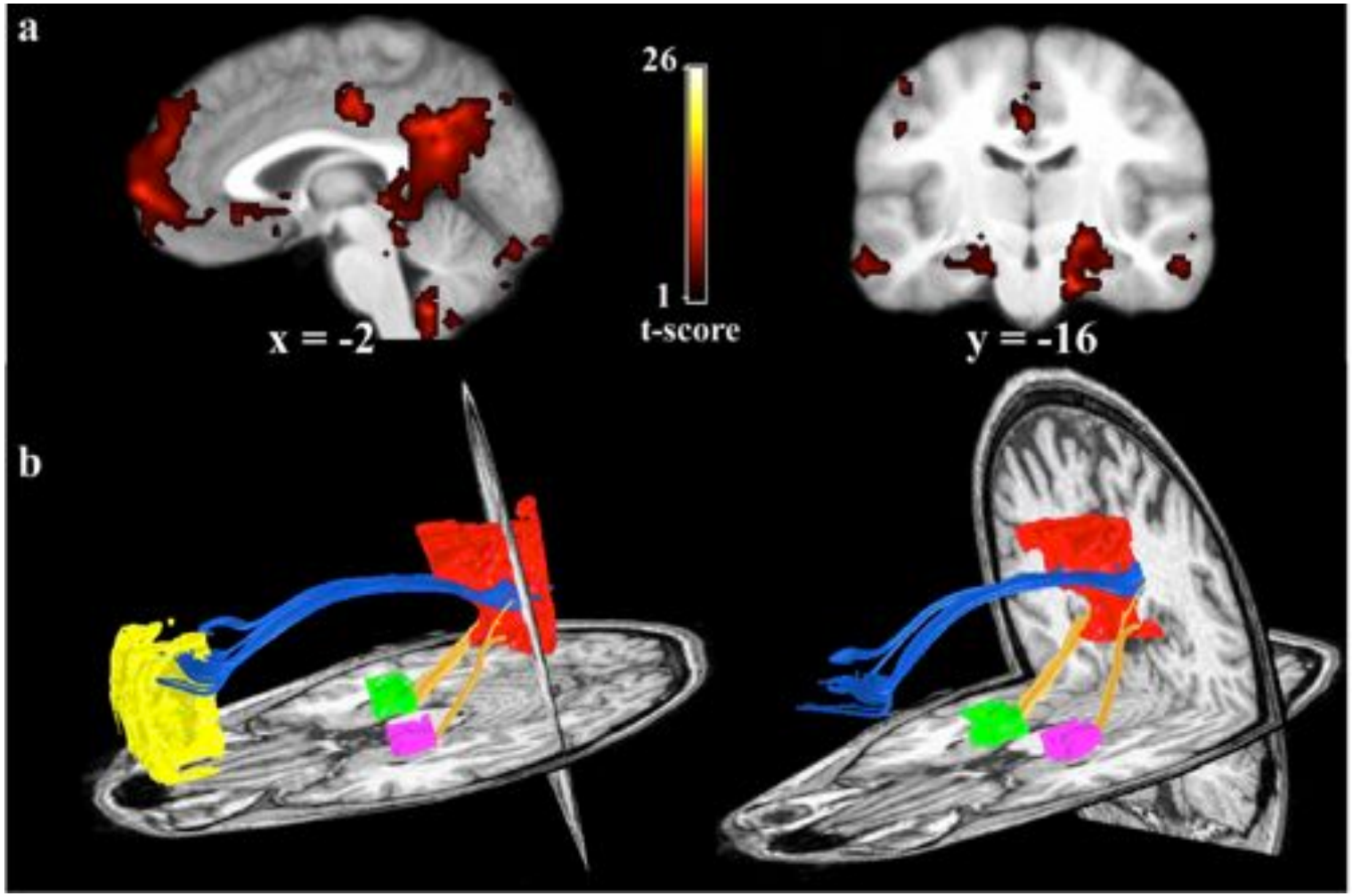




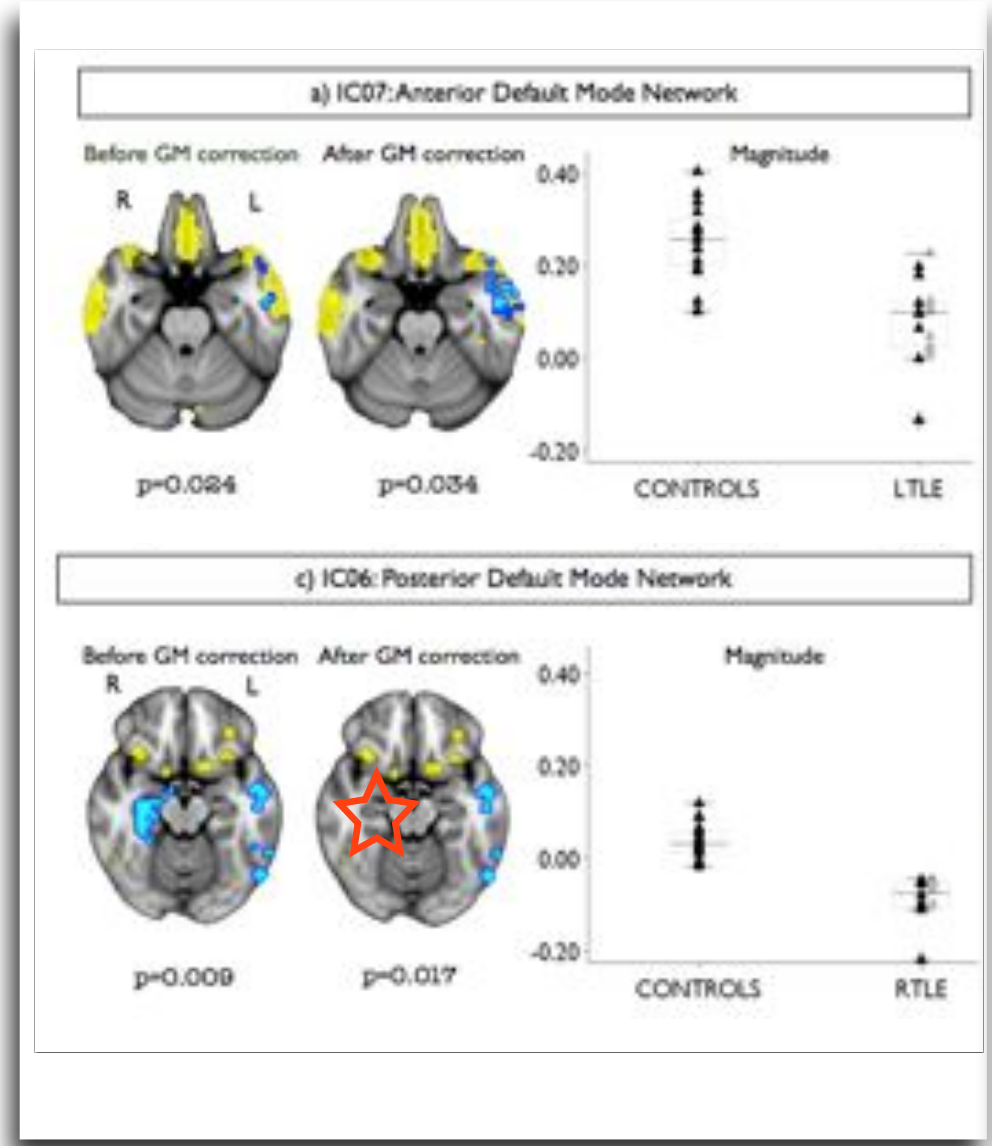
Smith et al. (2009)
PNAS

RSN connectivity: structural = functional

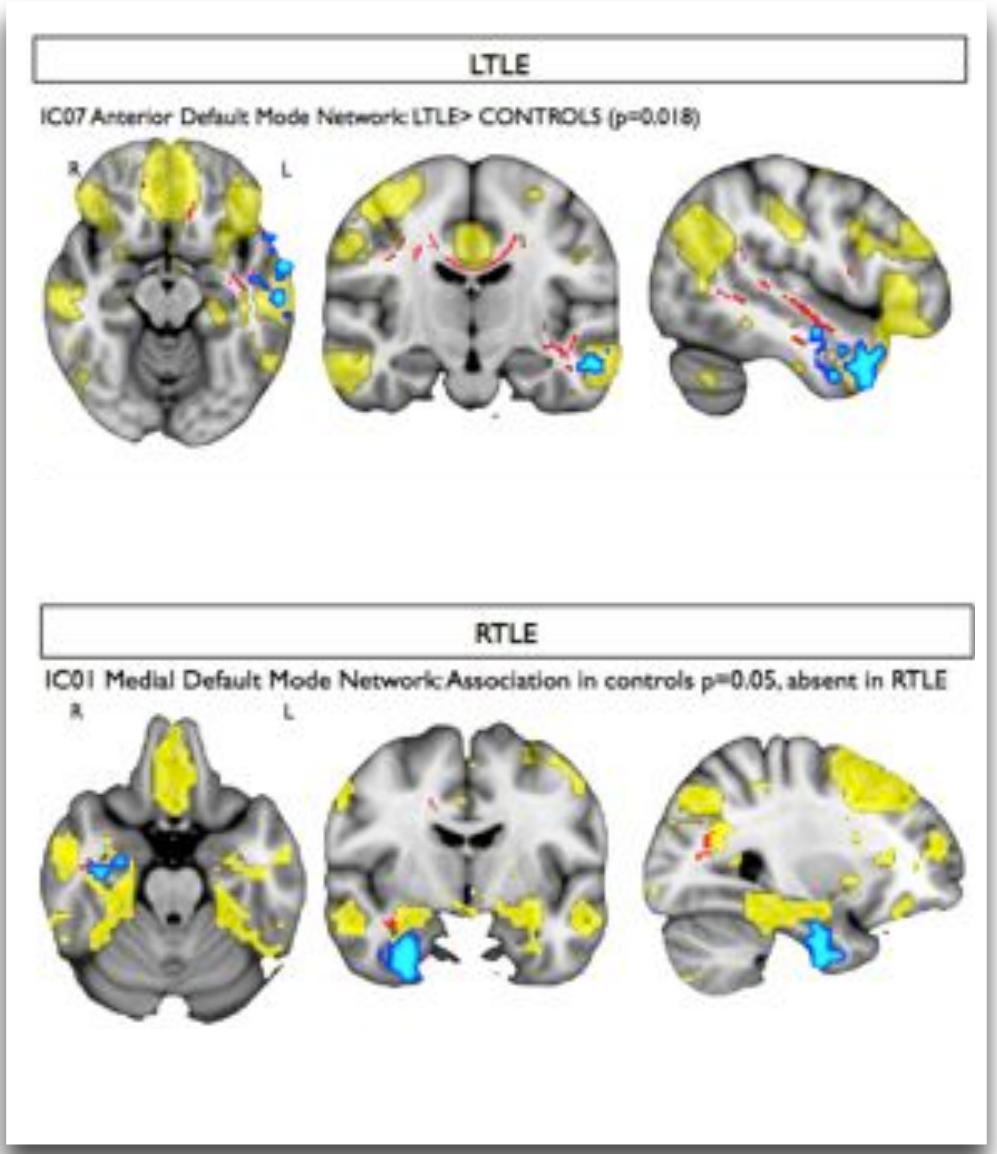


Greicius et al. (2008) *Cereb Cortex*

Grey Matter Density Confound

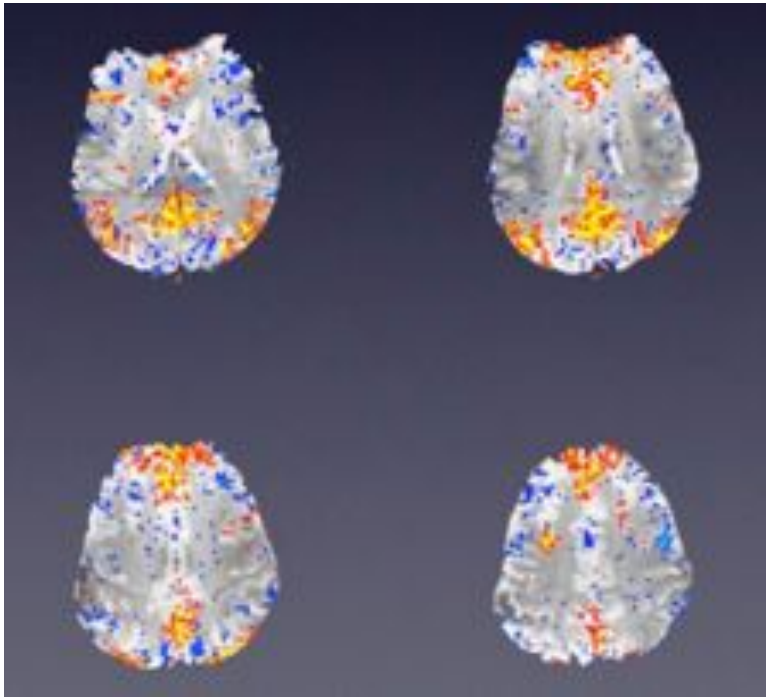


Correlation with white matter structure



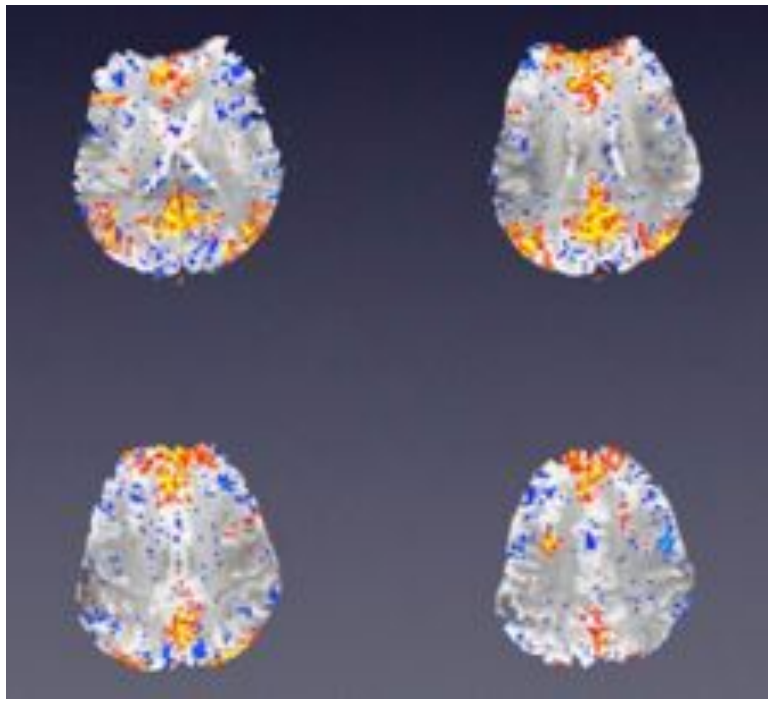
Voets et al. (2012) *Brain*

Resting-state FC analysis options



Resting-state FC analysis options

1. Seed-based correlation analysis (SCA)



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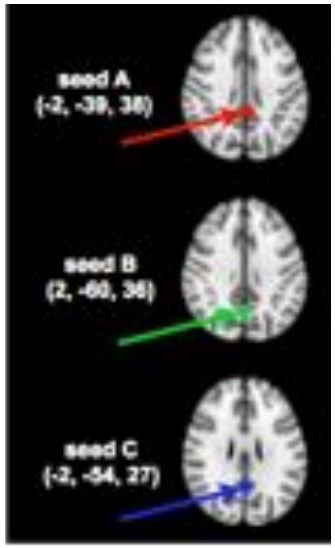

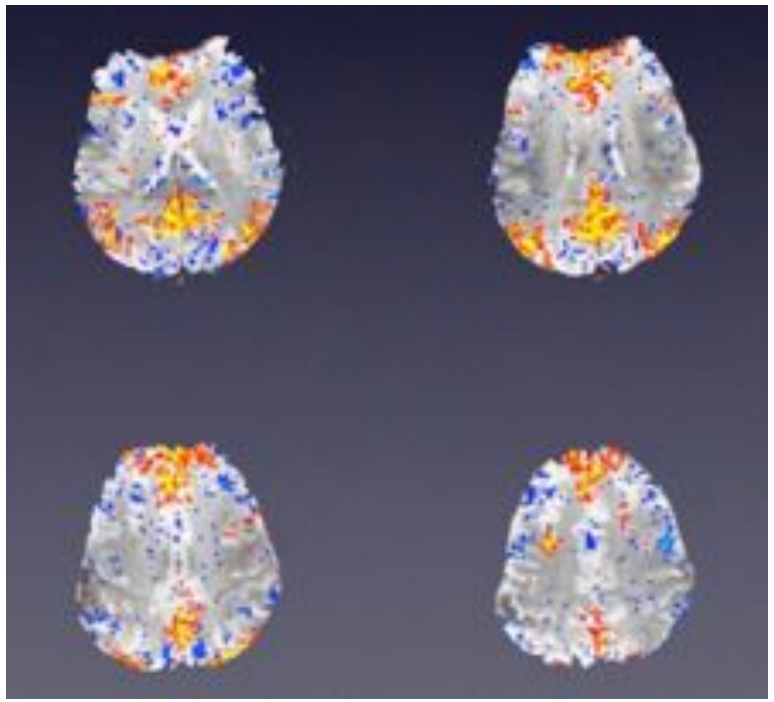

Resting-state FC analysis options

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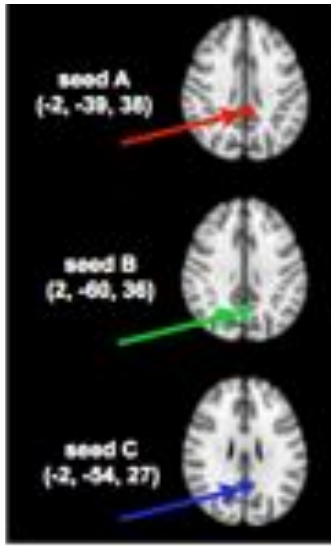
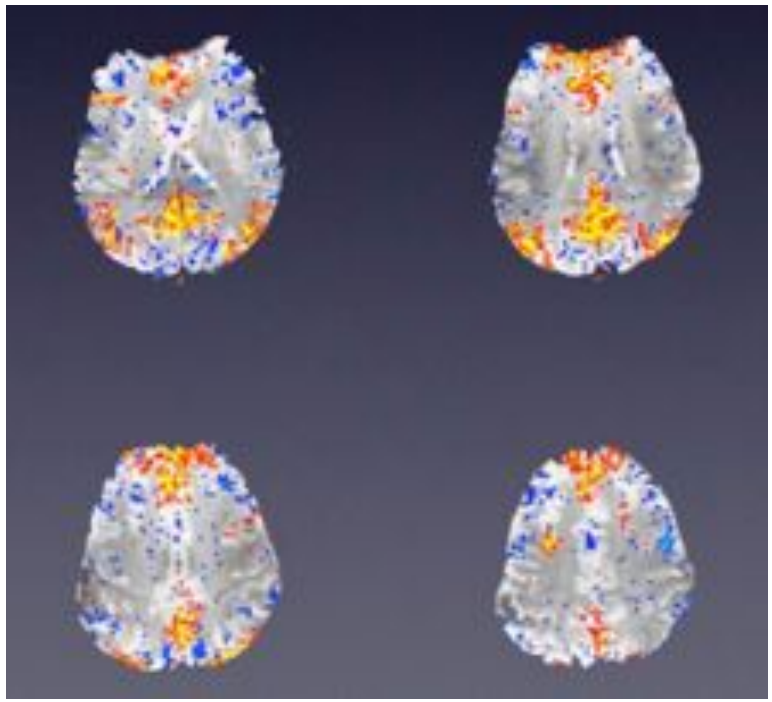


2. Independent component analysis (ICA)



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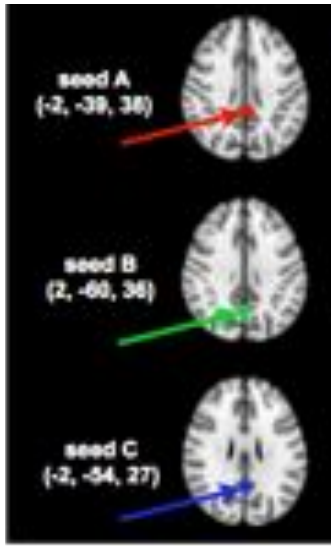

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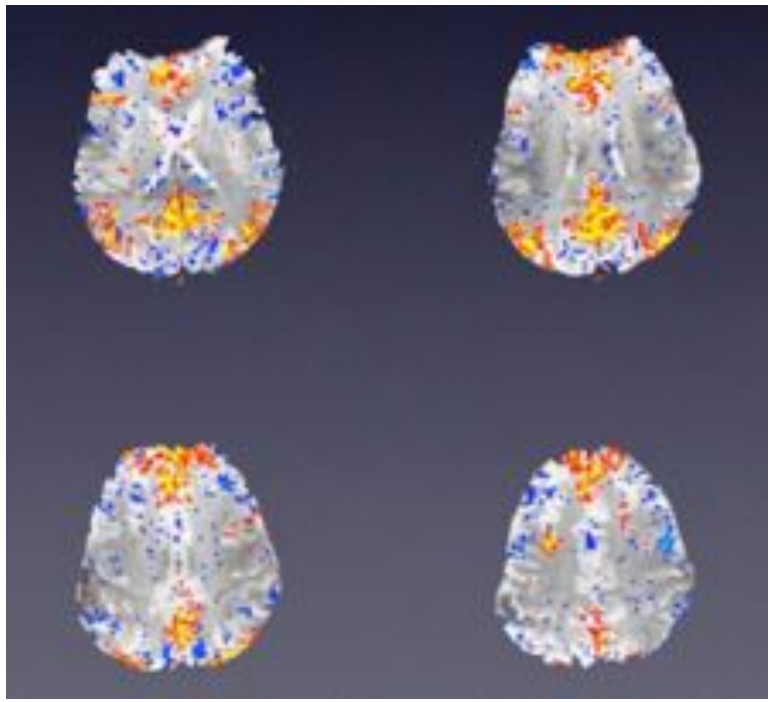
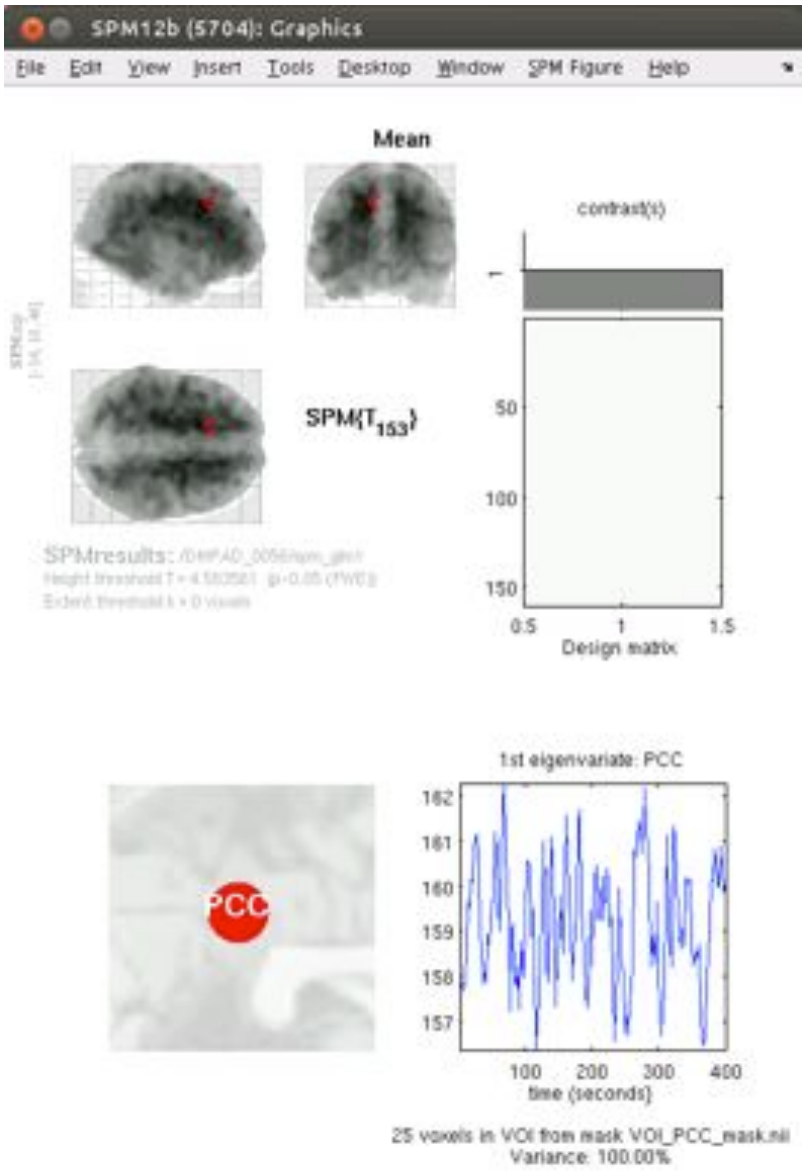


3. Psycho-/physio-physiological interaction (PPI) analysis?

SCA in SPM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Mean
contrast(s)
SPM{T153}
SPMresults:
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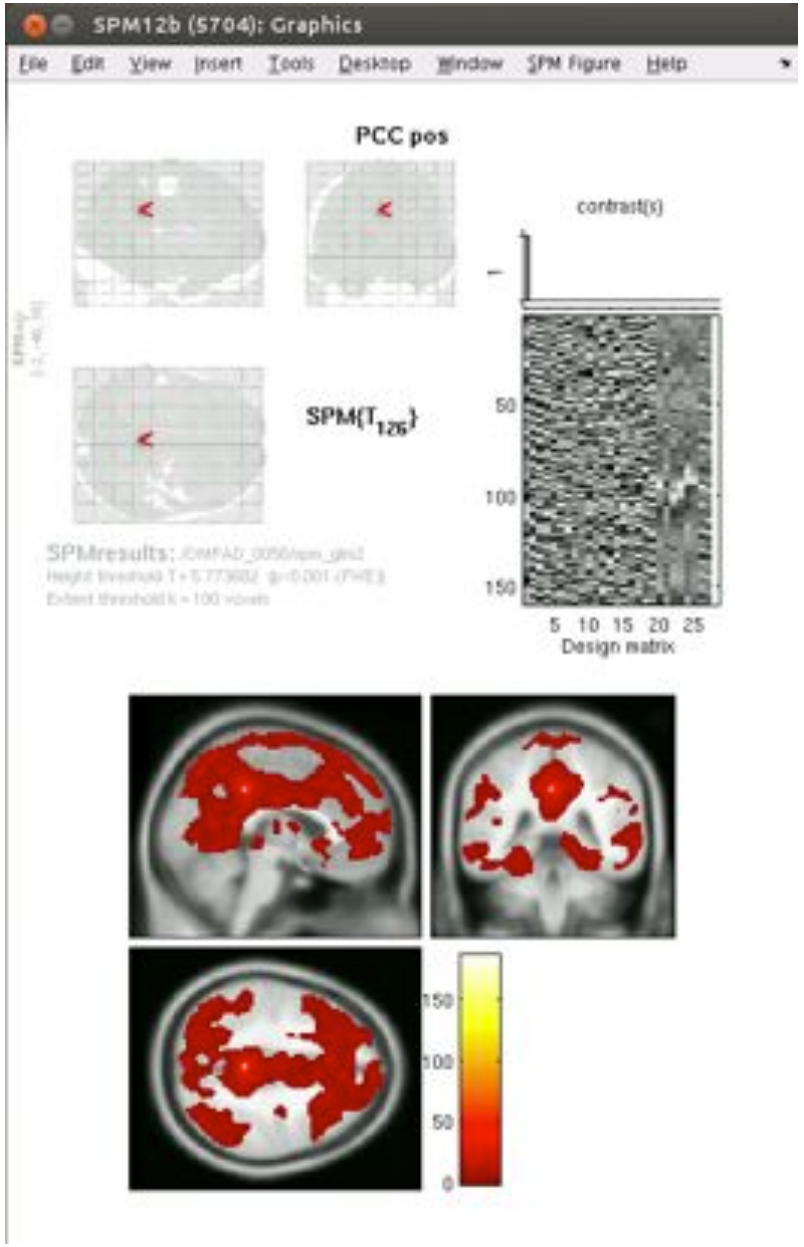
PCC
time (seconds)
25 voxels in VOI from mask VOI_PCC_mask.nii
Variance: 100.00%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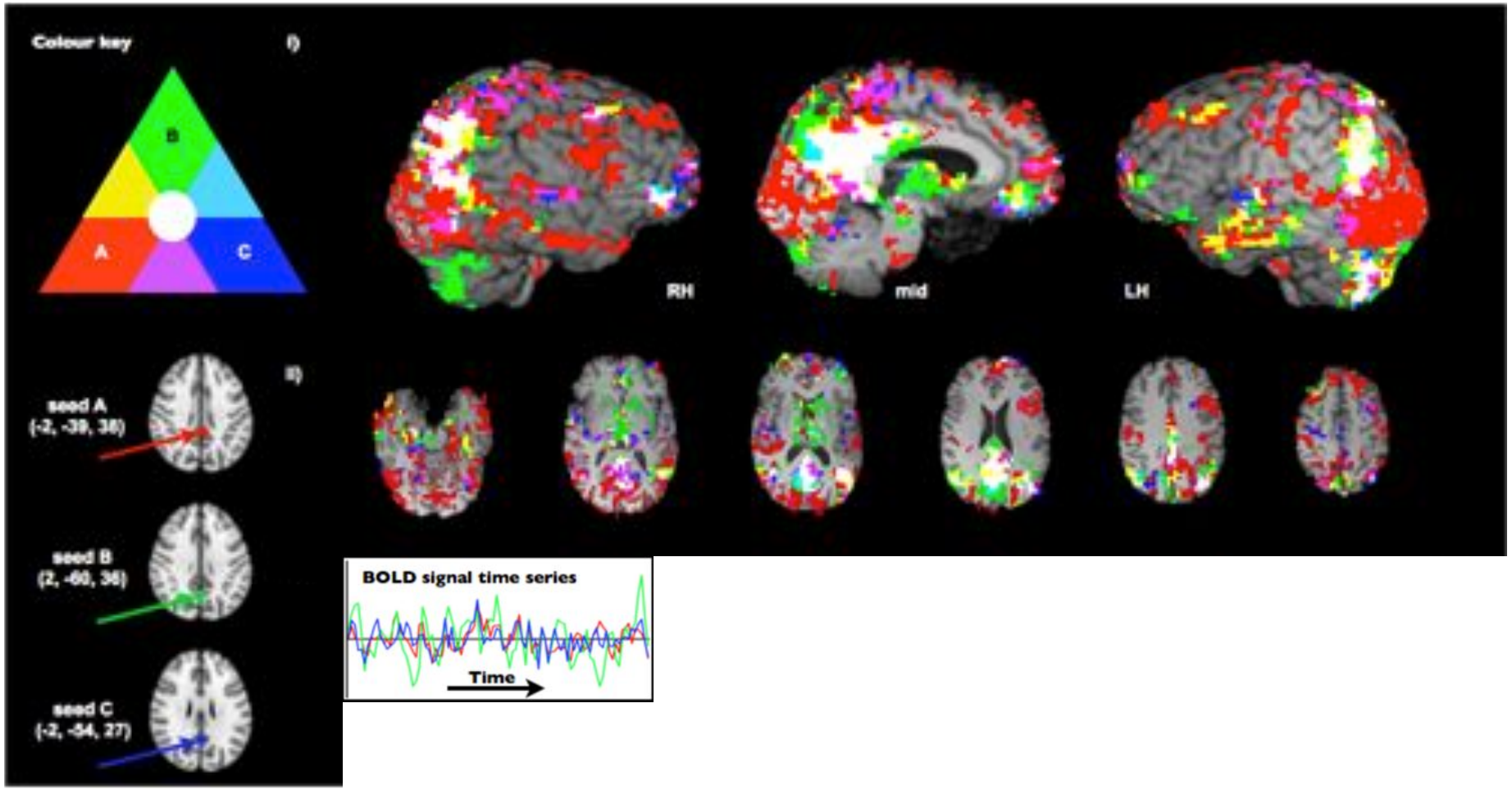
Design matrix

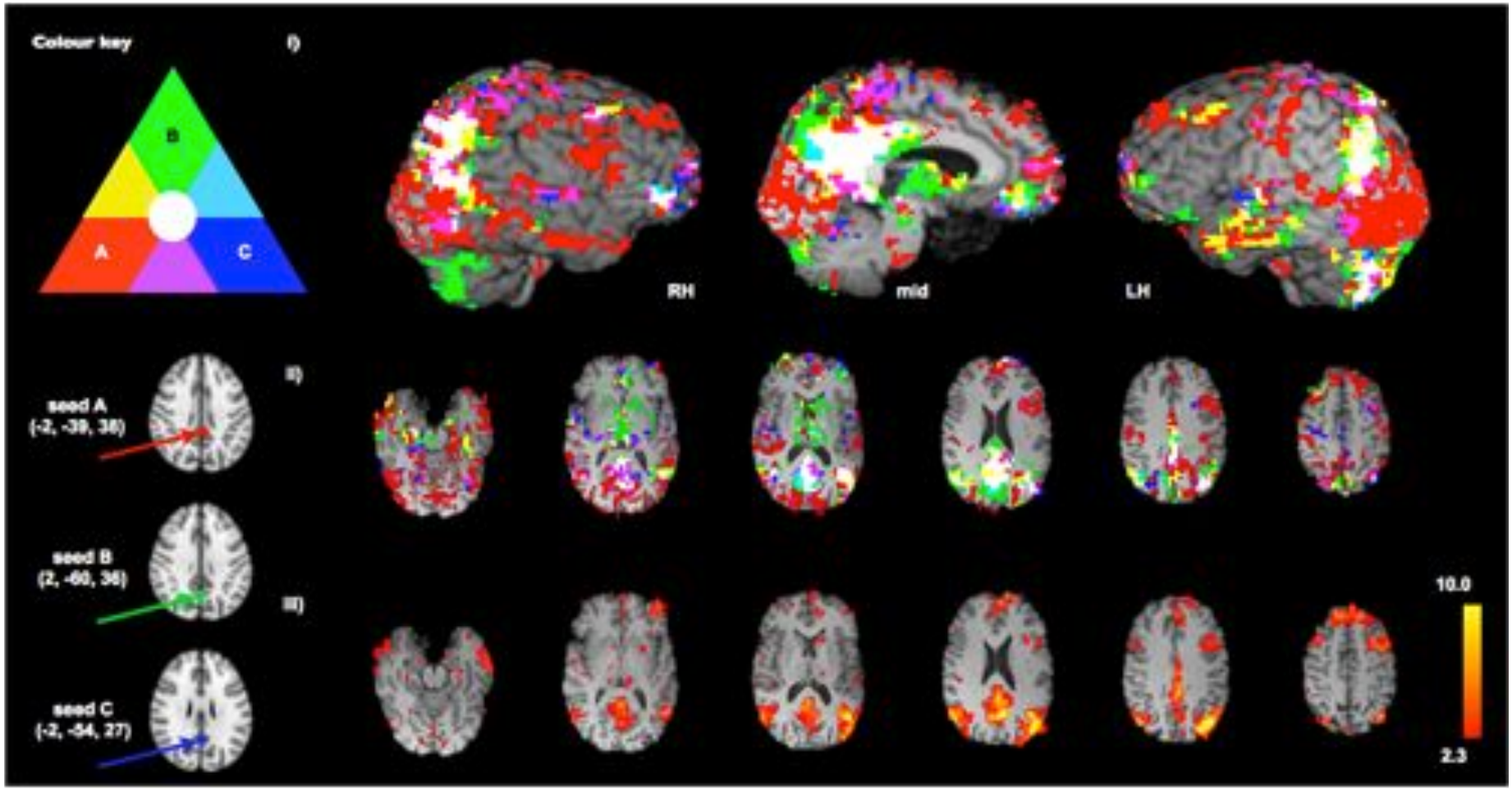
Analysis pros & cons: SCA



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

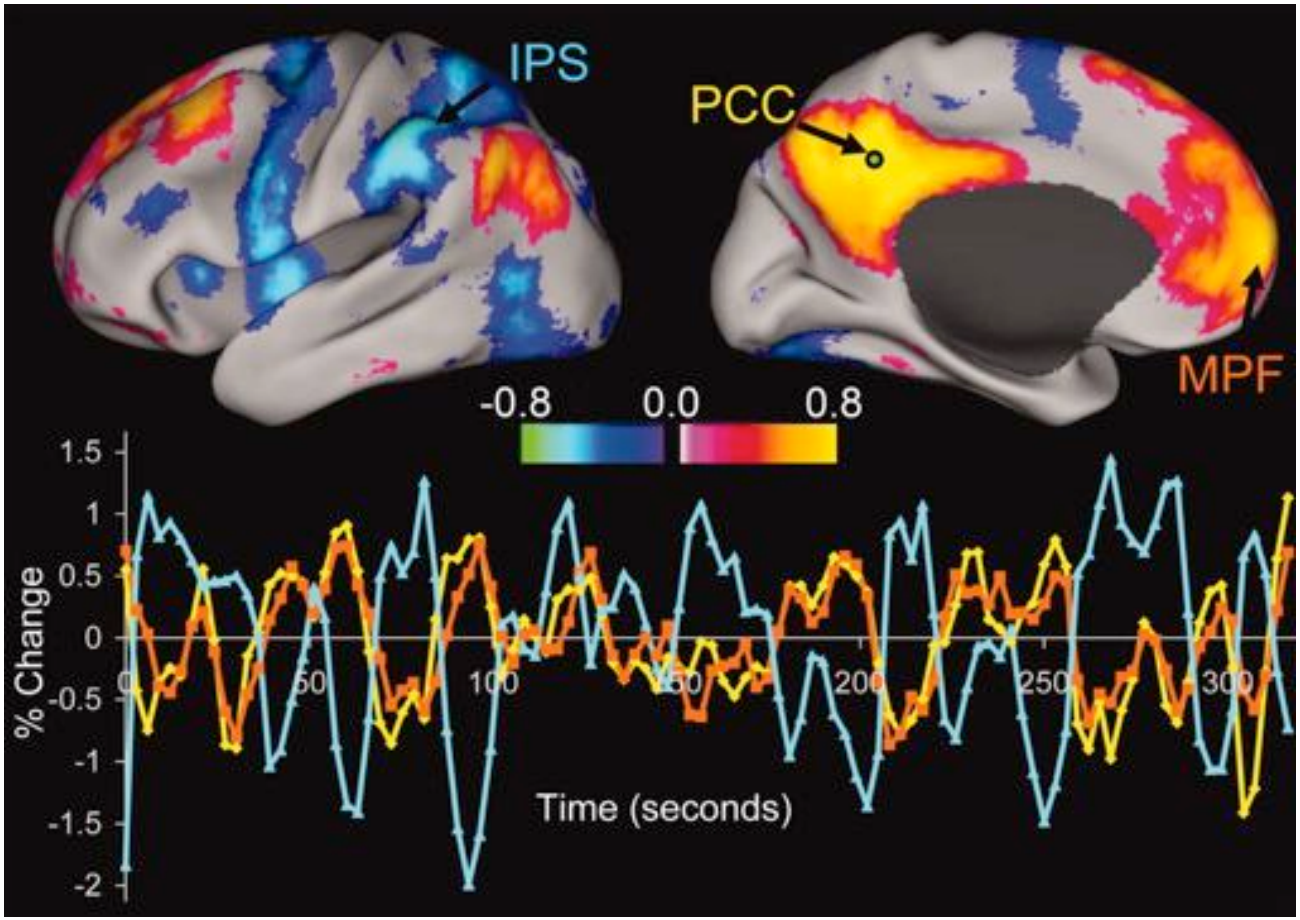
2. Independent component analysis: 'multivariate' approach

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

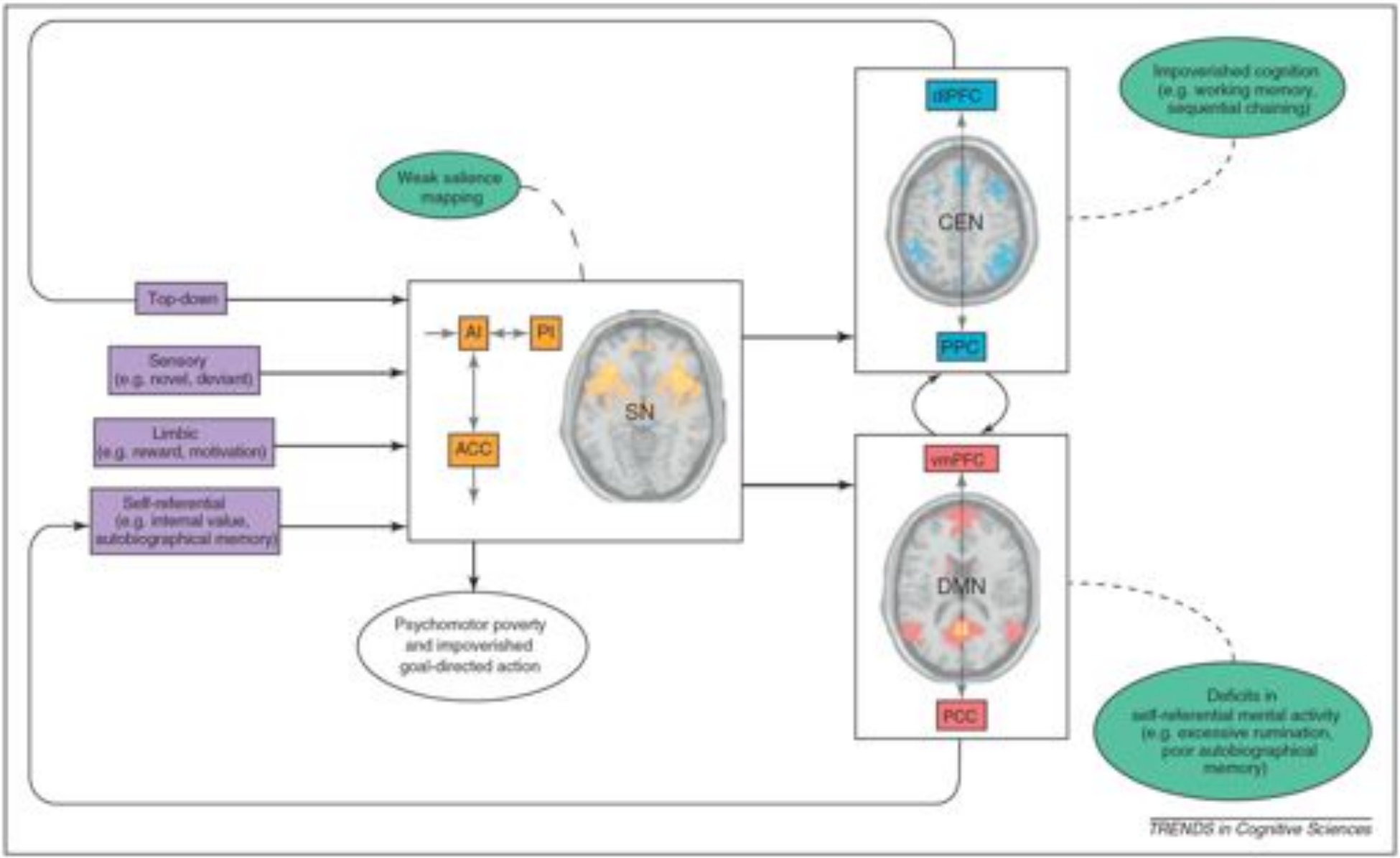
Between-network interactions

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



Fox et al. (2005)
PNAS

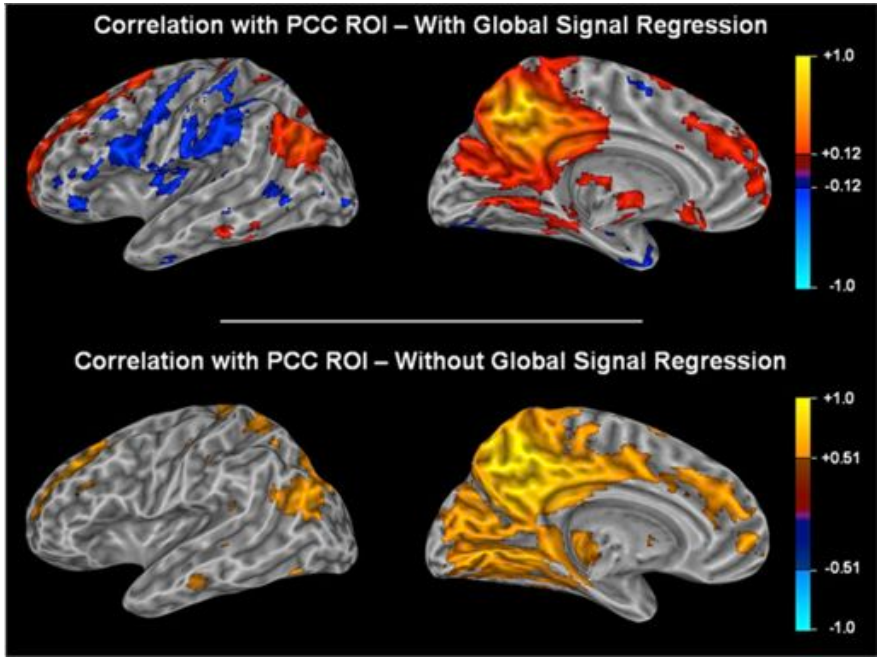
Between-network psychopathology model



Menon (2011) *TICS*

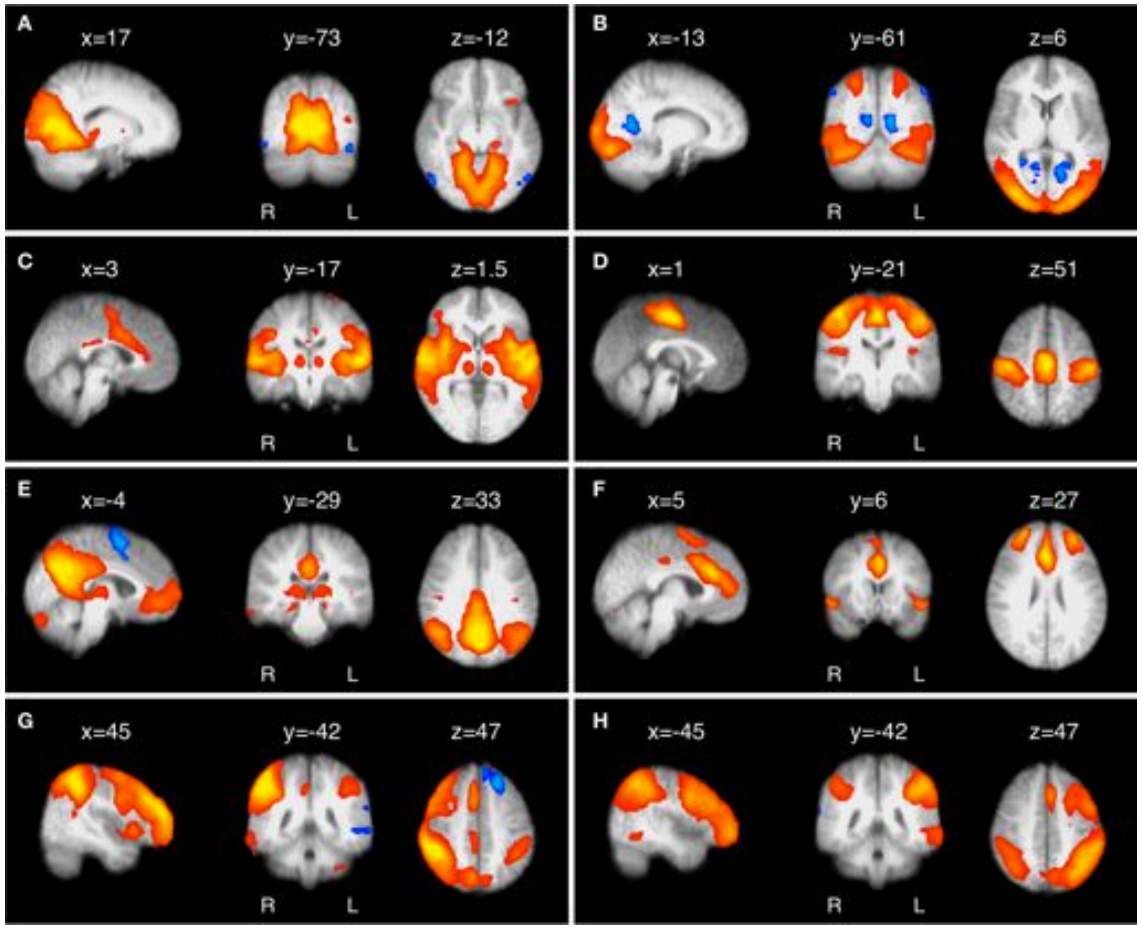
The dilemma of global signal regression

- 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)

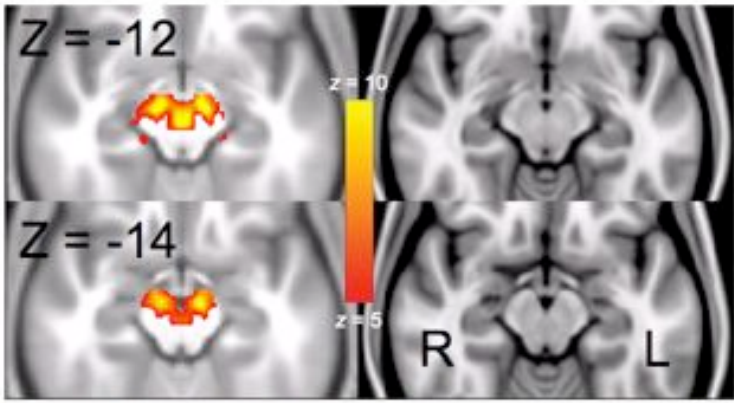


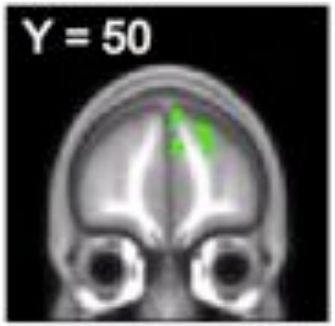
Beckmann et al. (2005) *Phil Trans R Soc Lond B*

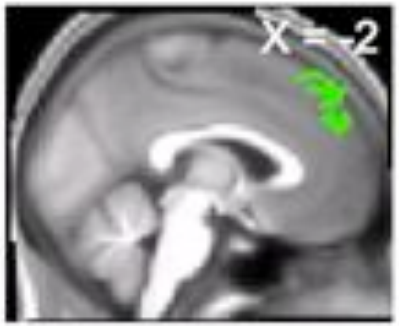
Independent component analysis (ICA)

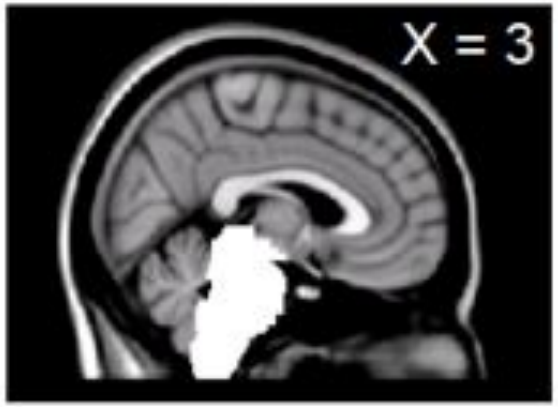
- Finds projections (components) of maximal independence in non-Gaussian data using higher-order (multivariate) statistics
- Multiple software packages for applying ICA to fMRI
  - FSL MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components)
  - GIFT
  - ICASSO...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

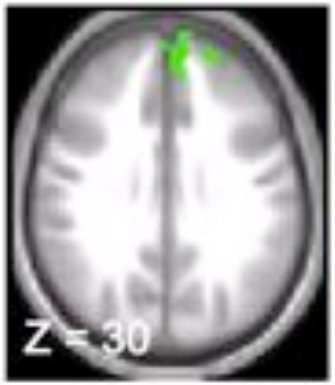
ICA-based parcellation

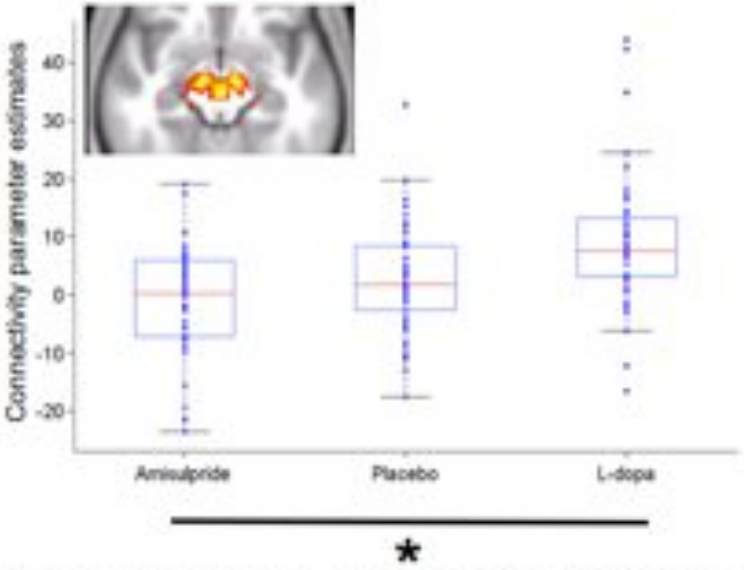












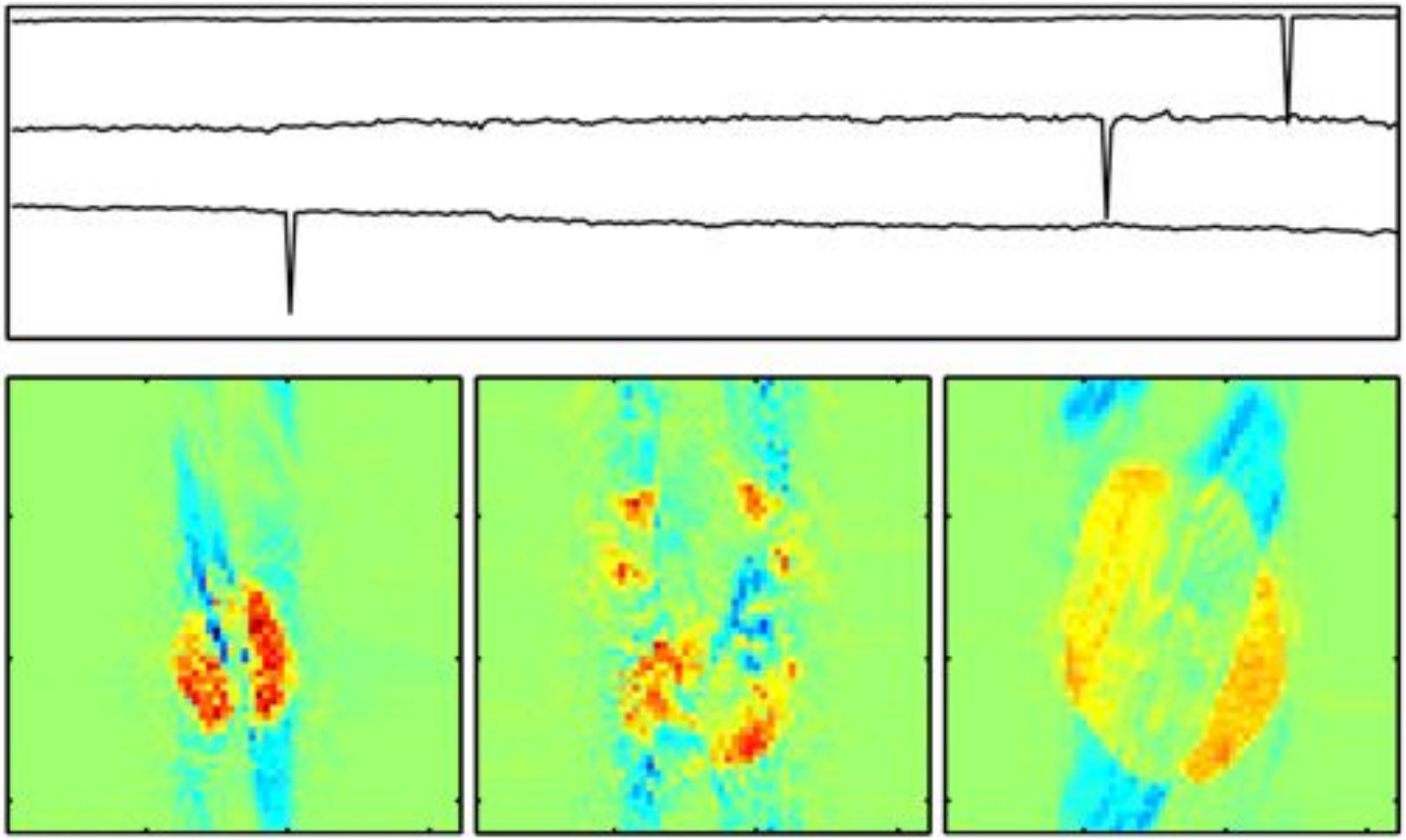
In preparation...

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 +

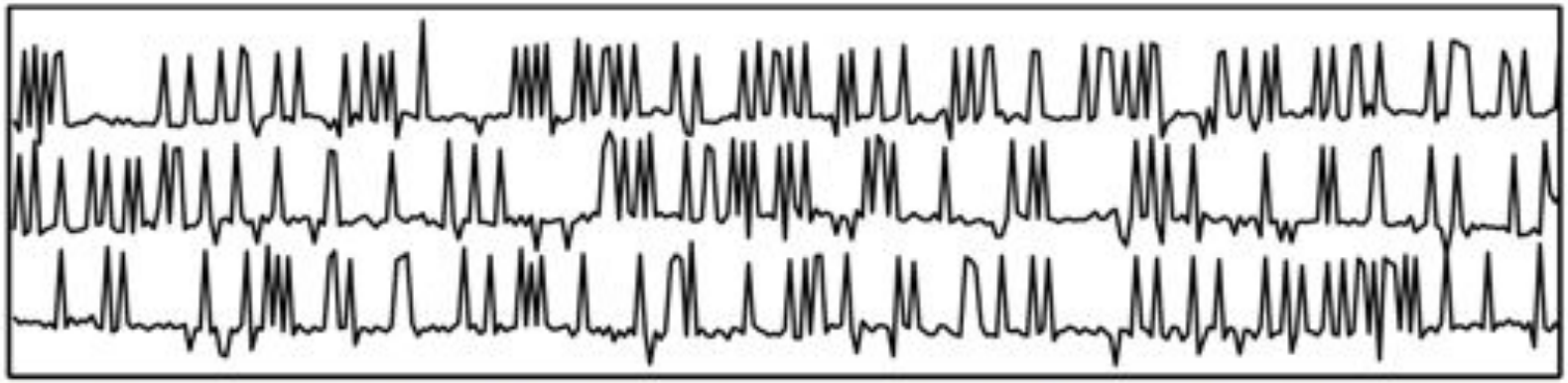
- Noise components
- slice ‘drop-outs’

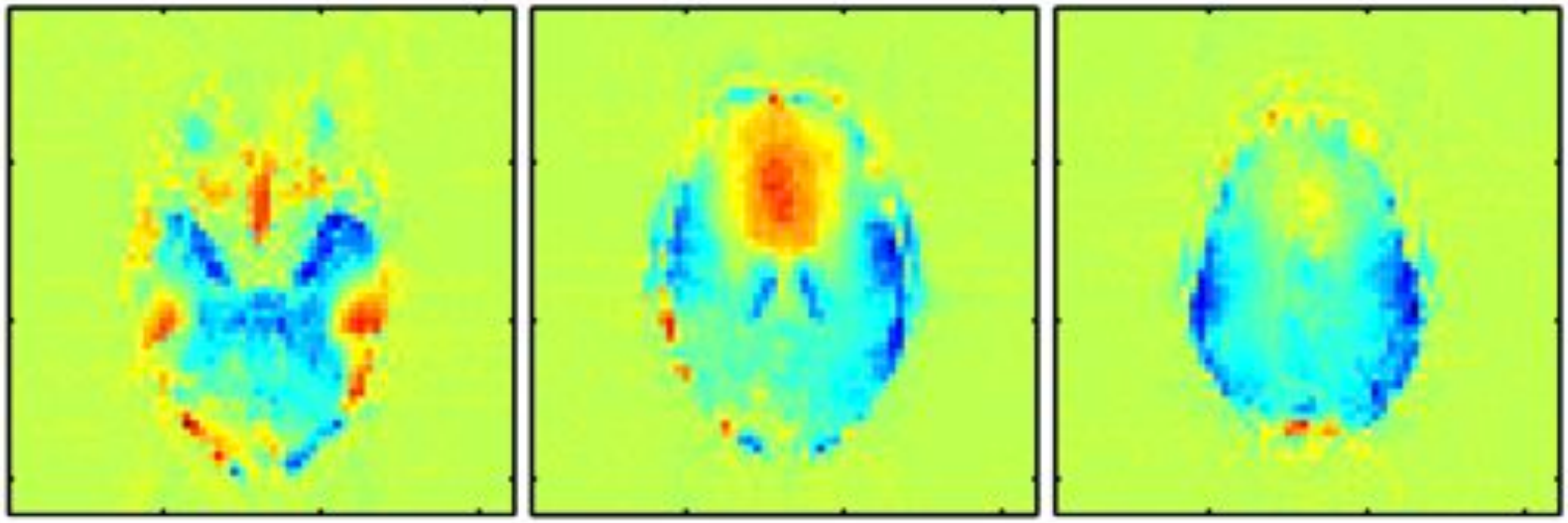


Thanks to C. Beckmann for examples

Analysis pros & cons +

- Noise components
- gradient instability

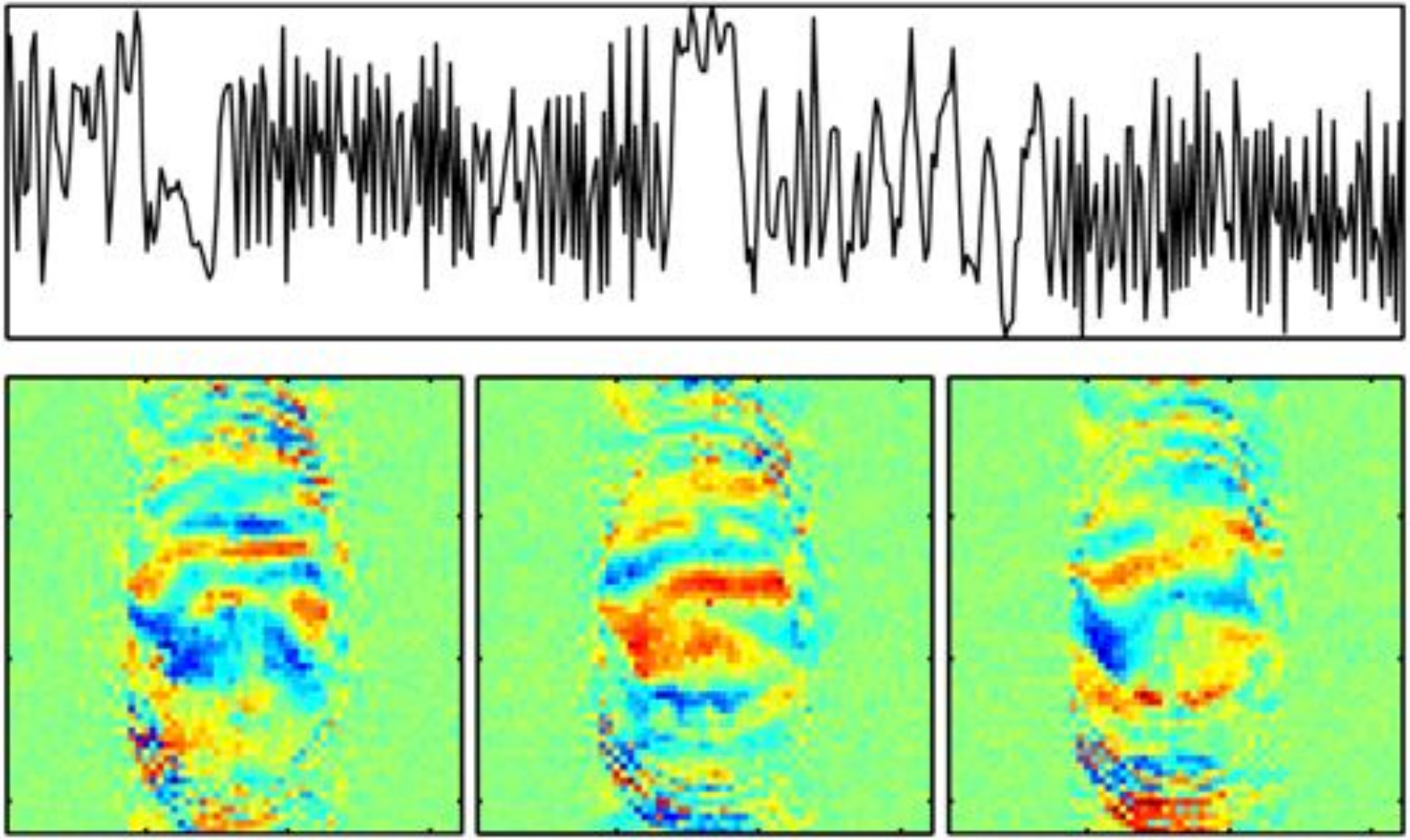




Thanks to C. Beckmann for examples

Analysis pros & cons +

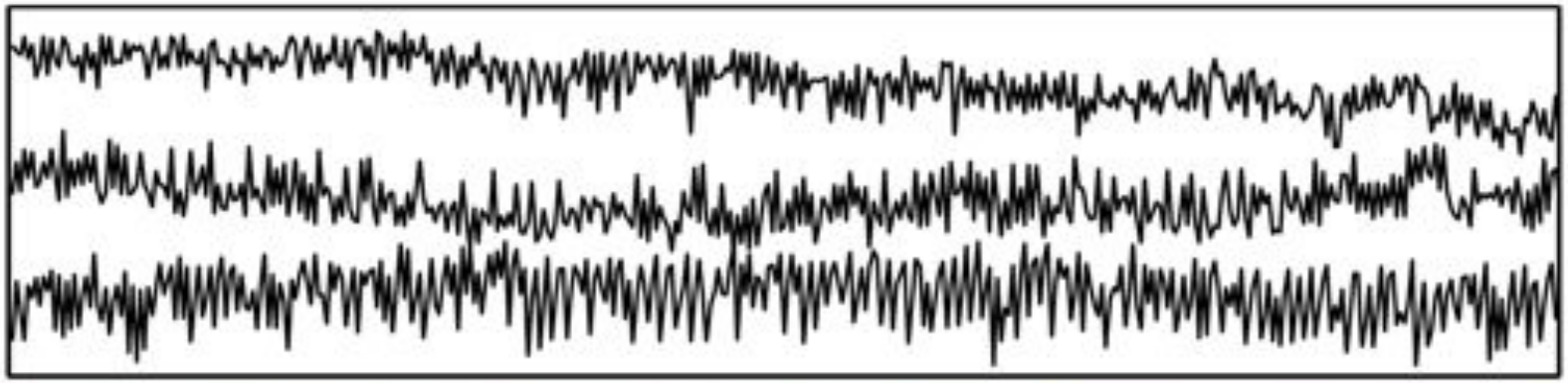
- Noise components
- EPI ‘ghost’ artefacts

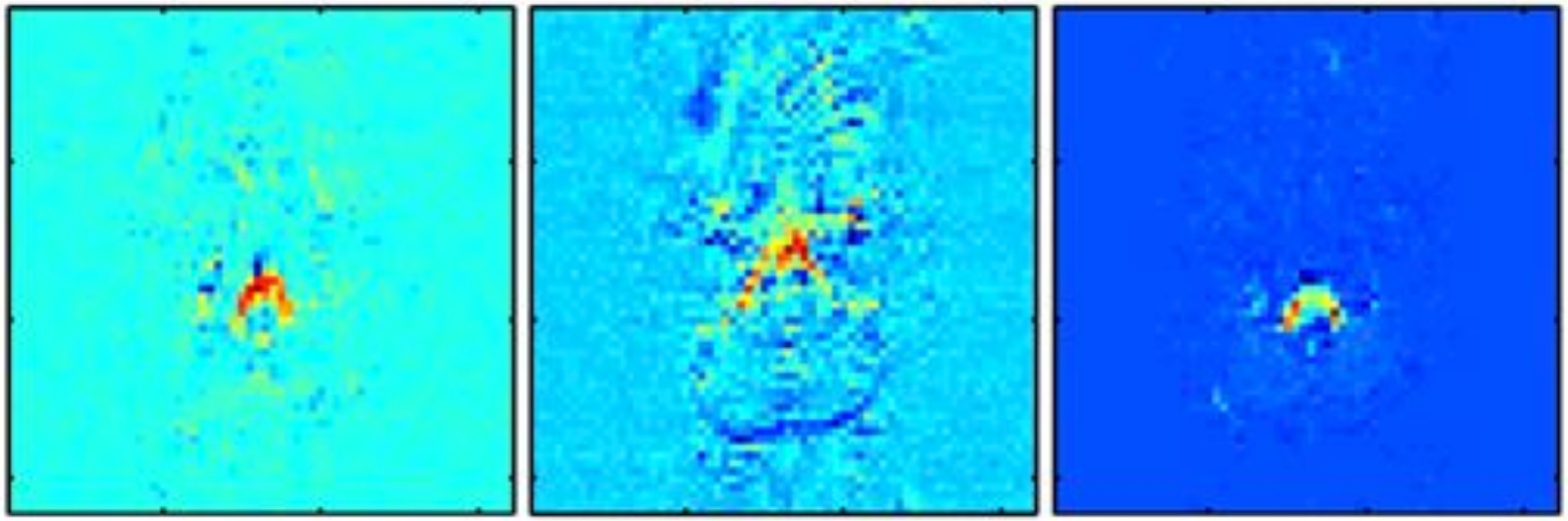


Thanks to C. Beckmann for examples

Analysis pros & cons +

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





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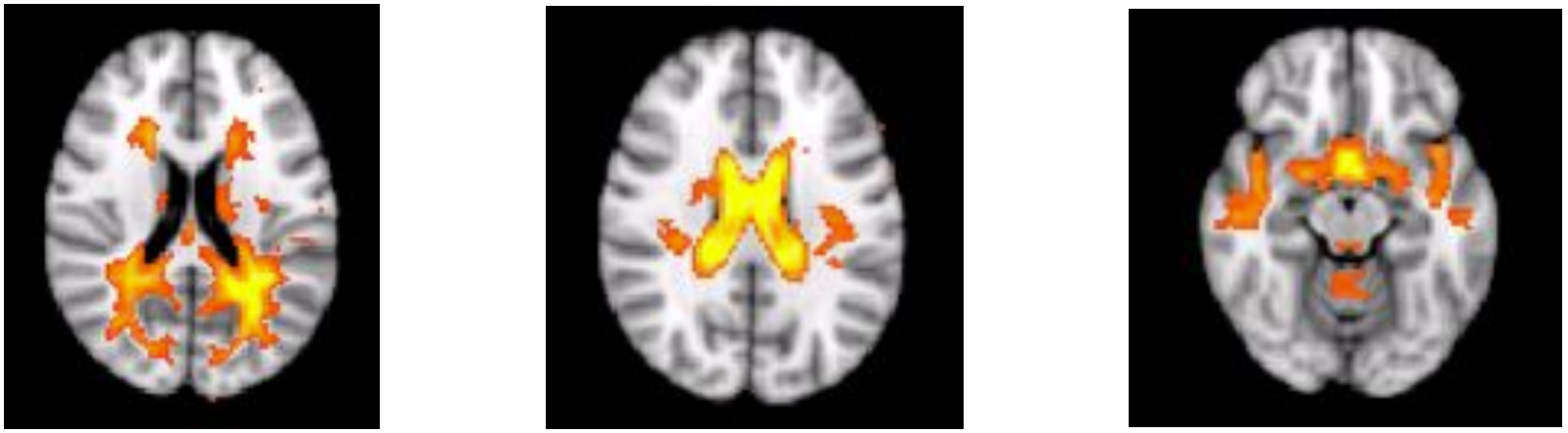
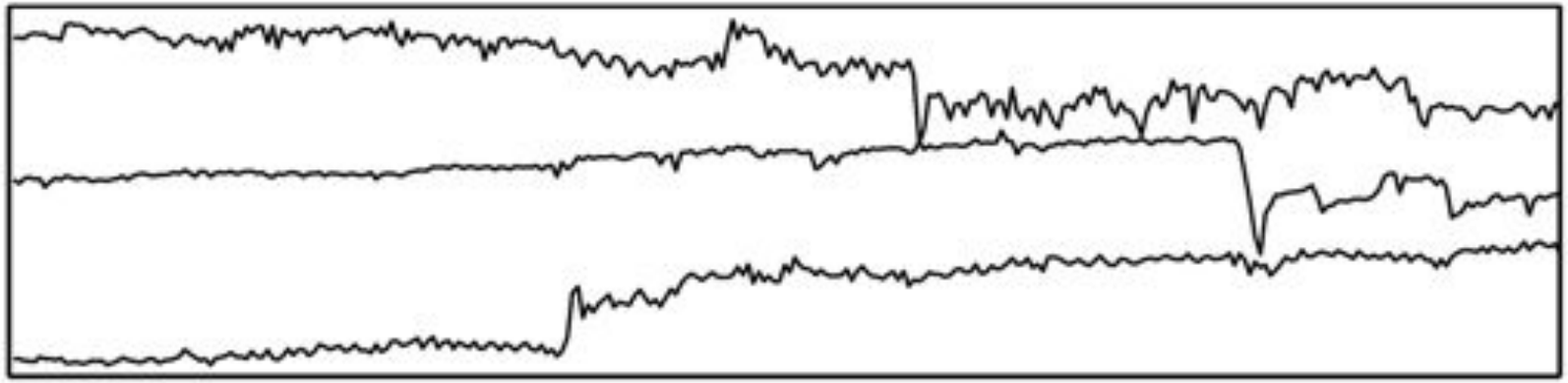
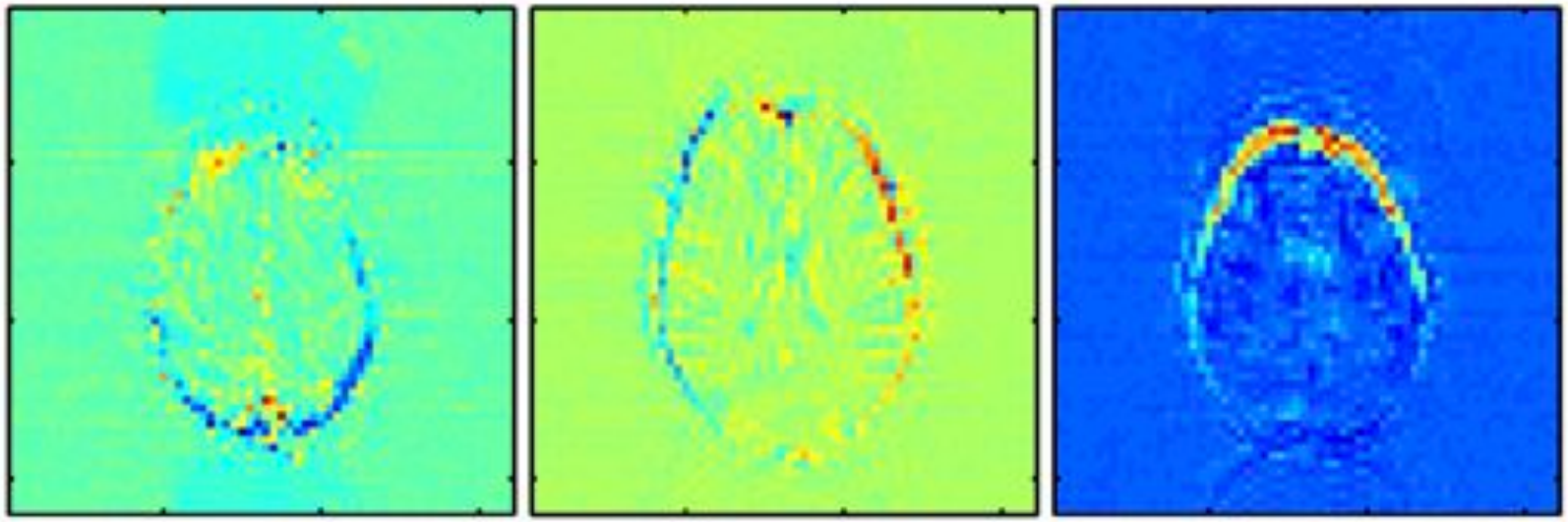
Analysis pros & cons +



Analysis pros & cons +

- Noise components
- Head motion

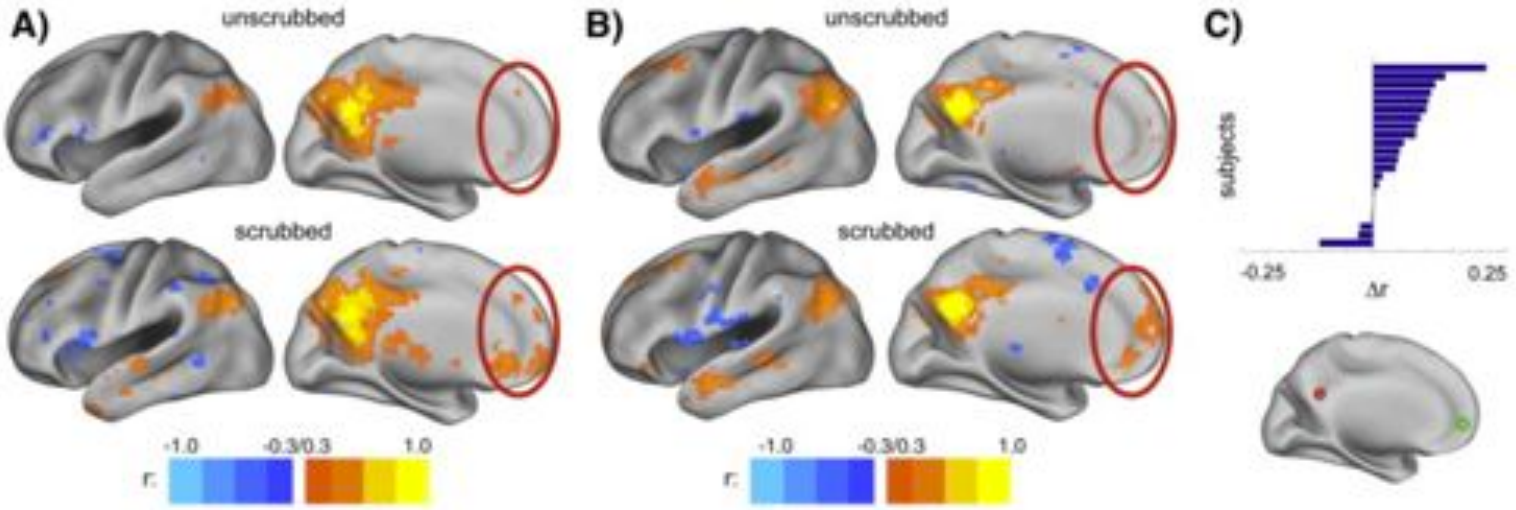




Thanks to C. Beckmann for examples

Motion aside...

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

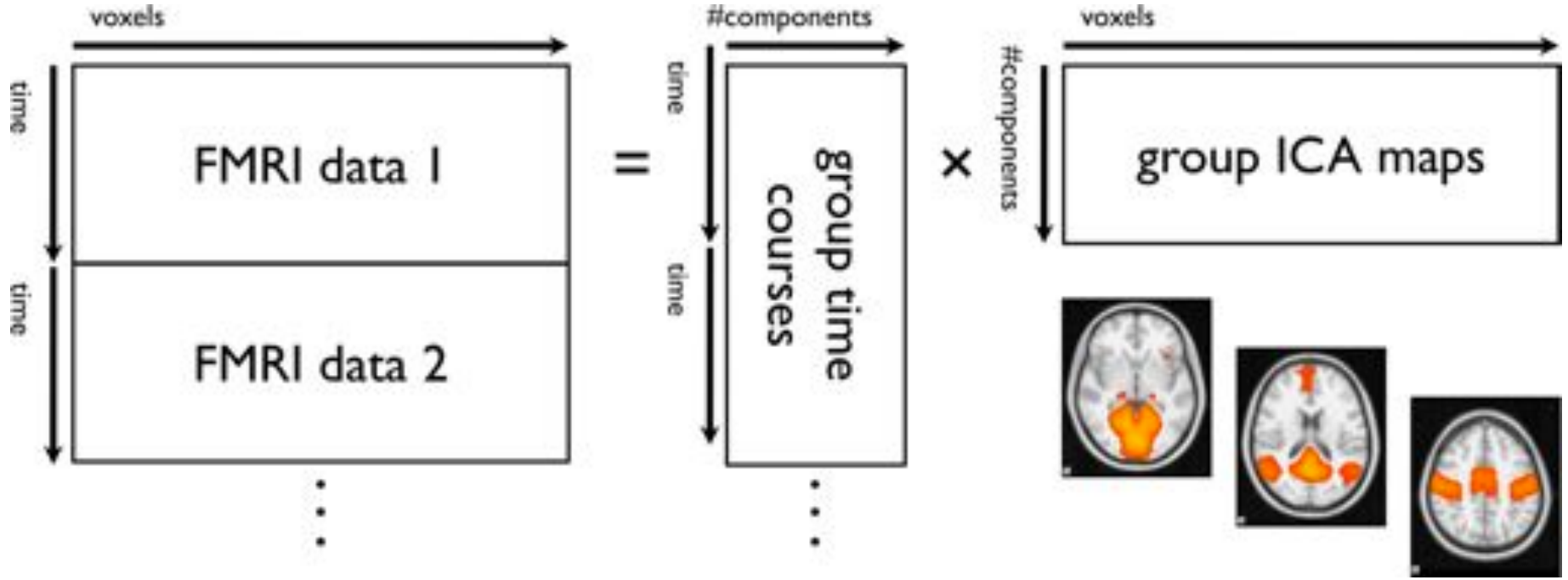


Power et al. (2012)
NeuroImage

Analysis pros & cons: ICA

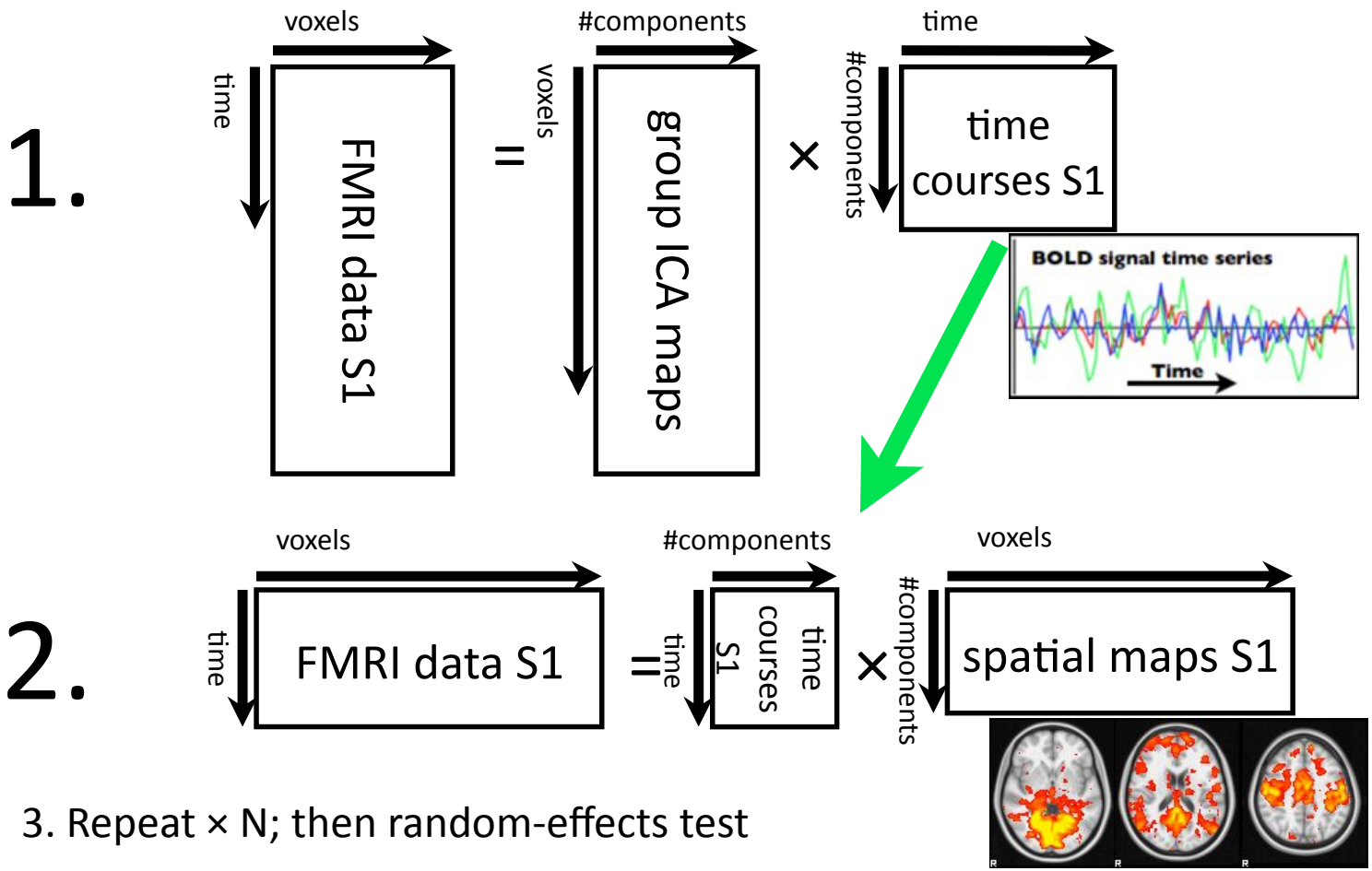
- ICA: Model order selection - what is the 'correct' number of components for a given data set?
- 'Splitting' / 'fusing' of components: levels of neurobiological complexity, or mathematical 'crowbarring'?
- How does one decide which components are 'of interest'/functional relevance/neuronal in origin?
- Nonstationarity again... Temporal ICA? - Smith et al (2012) *PNAS*

Multi-session RSN identification: concat-ICA



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

Multi-session RSN *comparison*: dual regression

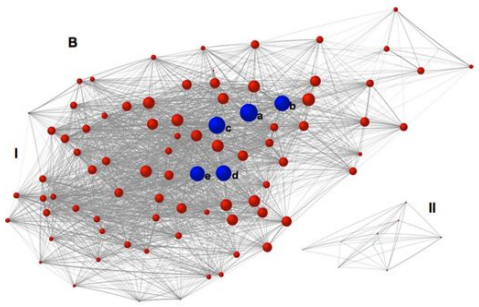


3. Repeat × N; then random-effects test

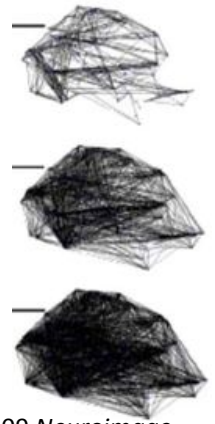
Filippini et al. (2009) *PNAS*; Beckmann et al. (2009) *OHBM [abstr]*

Alternative methods

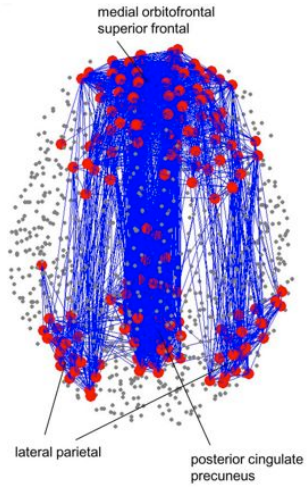
- Graph theoretical approaches
  - 'Nodes' & 'Edges'
  - What's your cut-off point?
- Amplitude of low-frequency fluctuations (ALFF)
- Regional homogeneity (ReHo)
- Clustering



Buckner et al. '09 *J Neurosci*



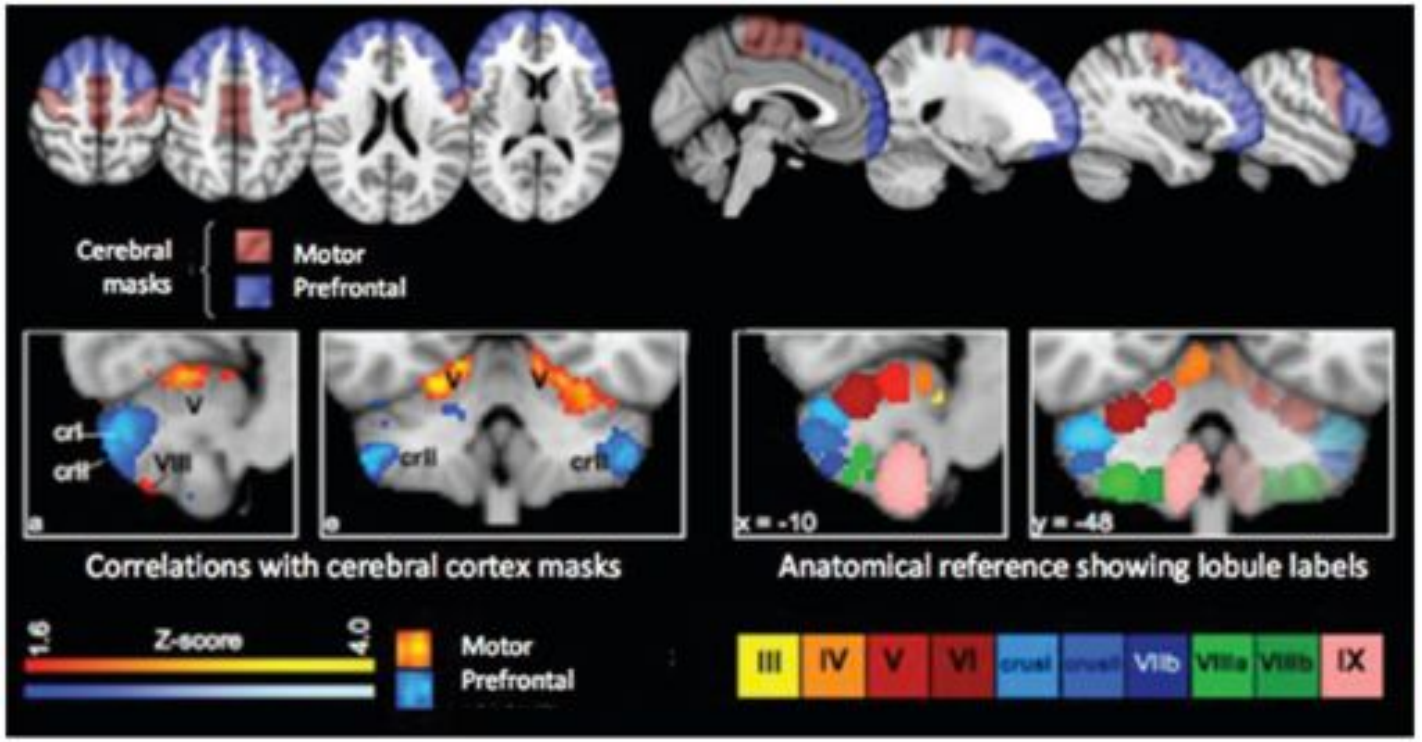
Bullmore et al. '09 *Neuroimage*



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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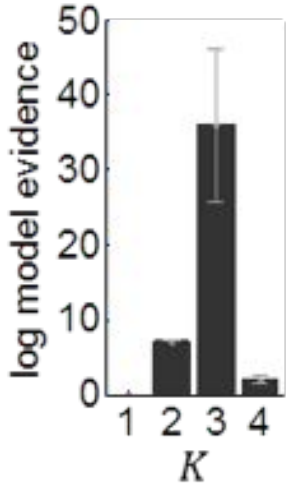
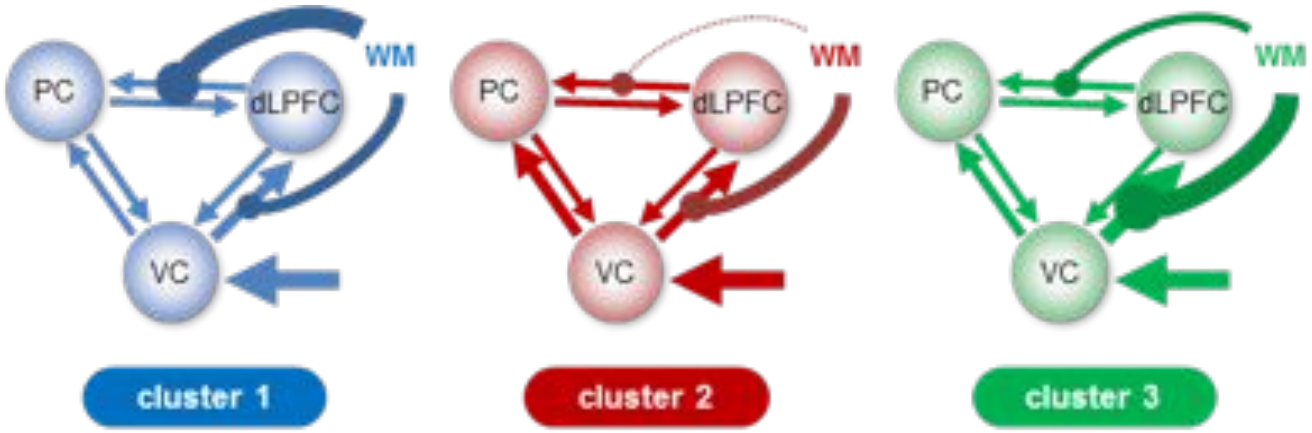
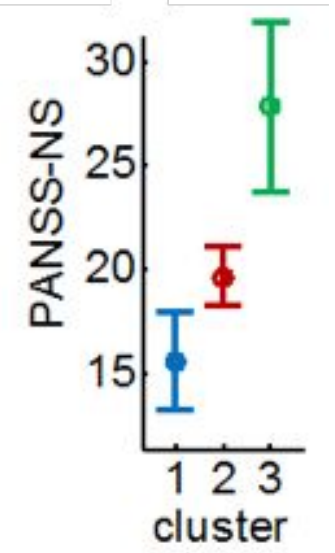
Detecting subgroups of patients in schizophrenia

Optimal cluster solution



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

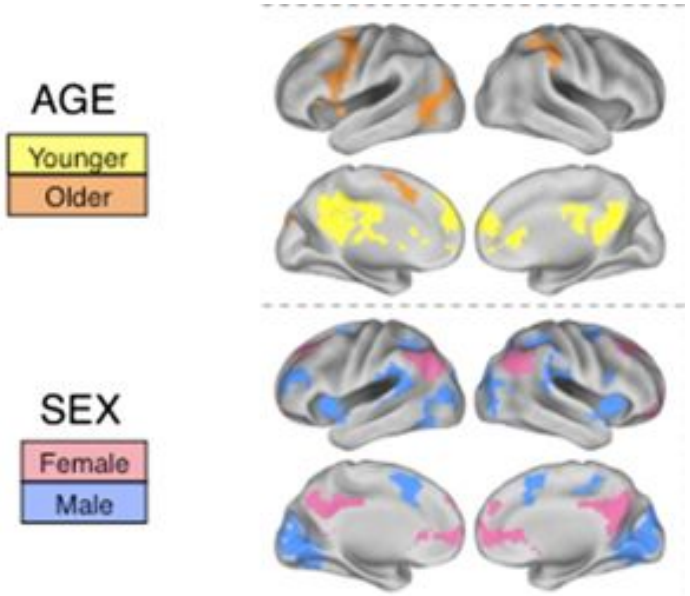




Brodersen et al (2014) *Neuroimage: Clinical*

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

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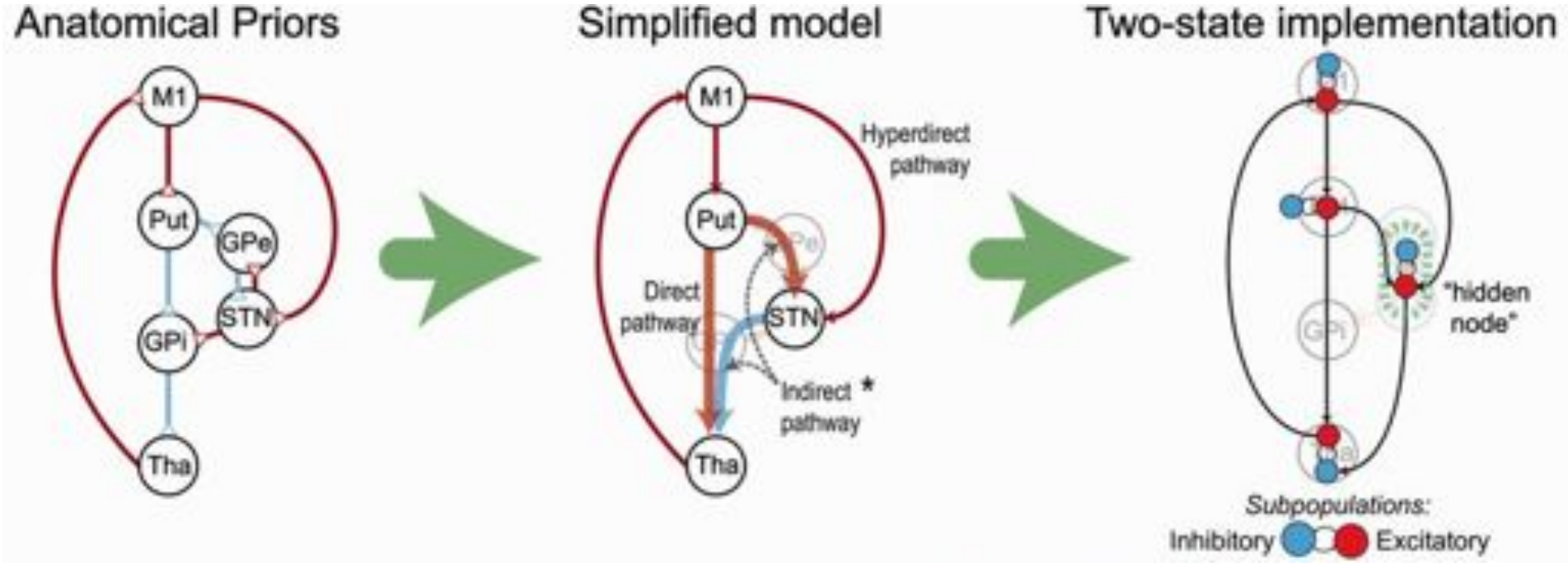
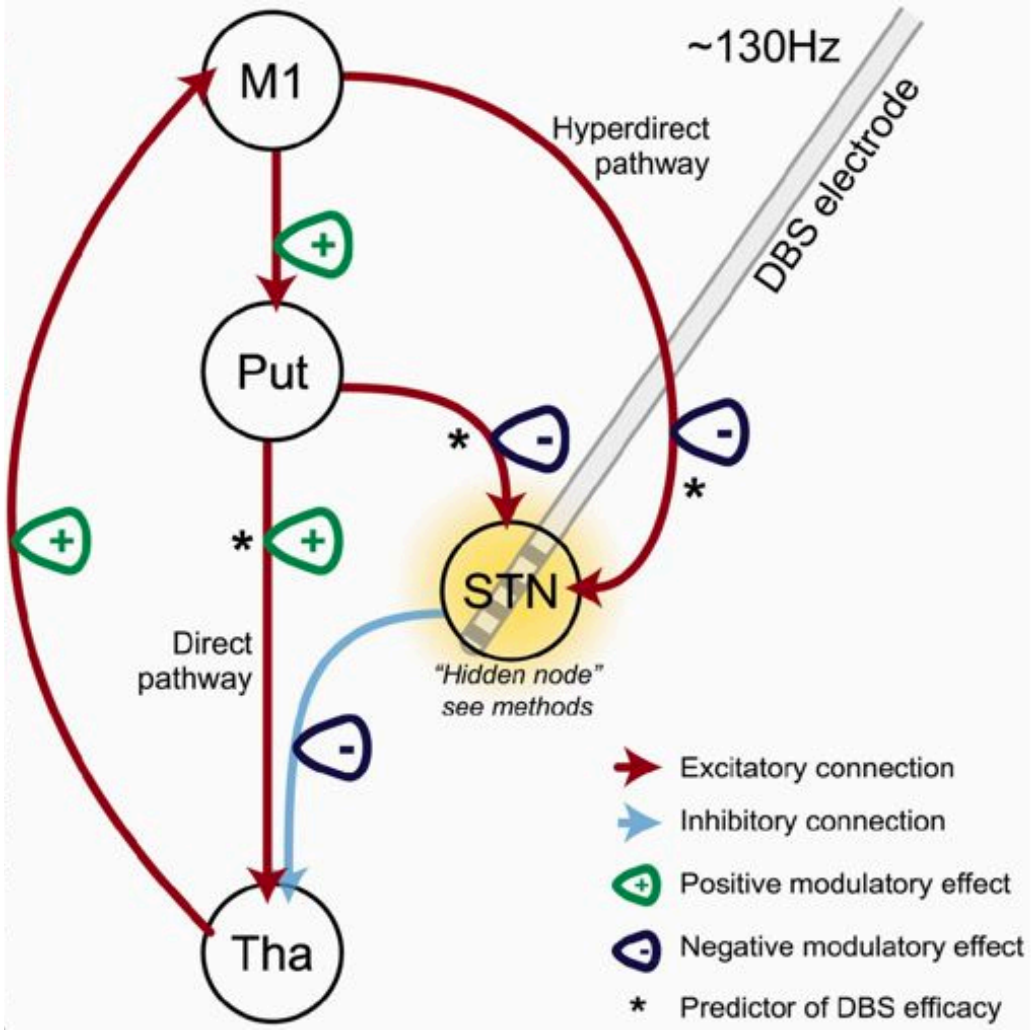
‘Mechanistic’ analysis of resting-state fMRI data



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