

Resting-State Functional Connectivity MRI: Principles and Clinical Applications in Dementia



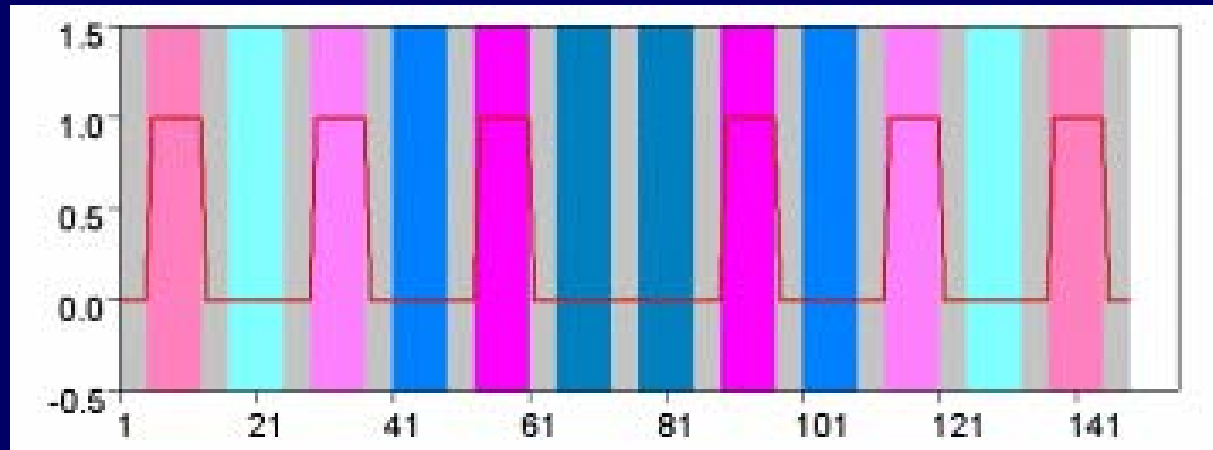
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Department of Neurology and Neurological Sciences
Stanford University School of Medicine

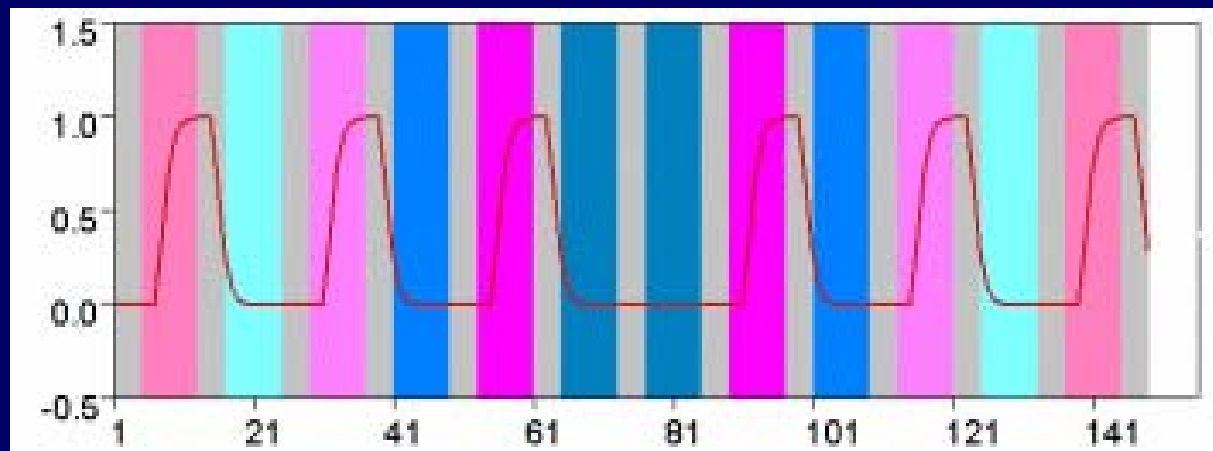
Overview

- Deactivation and the default mode
- Functional connectivity/resting-state fMRI
- Applications in AD
- Other networks/other neuropsychiatric disorders

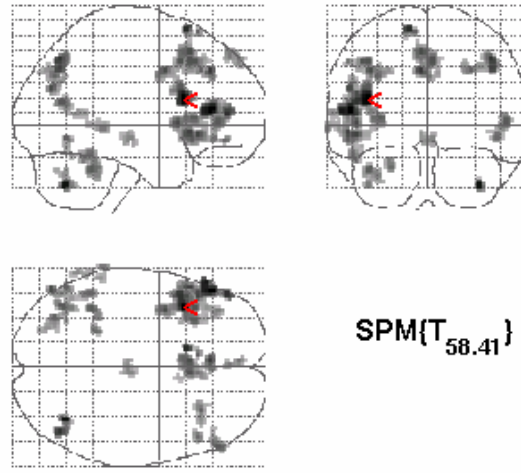
Task-Activation fMRI



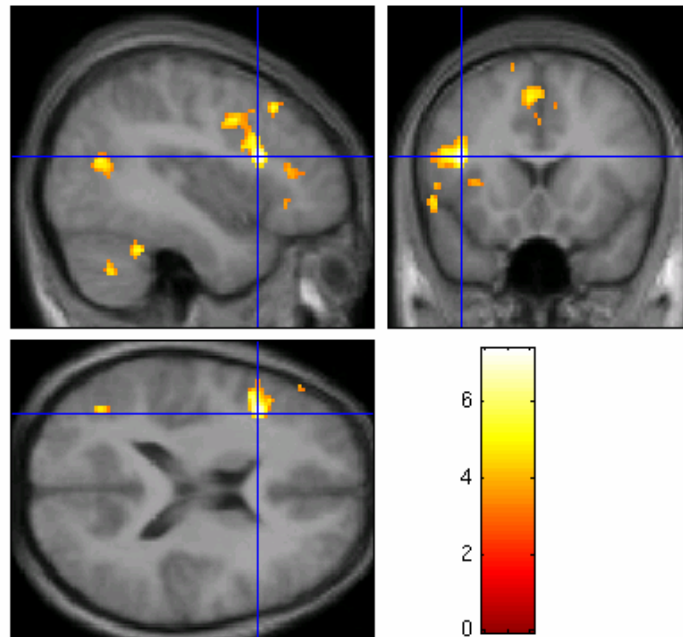
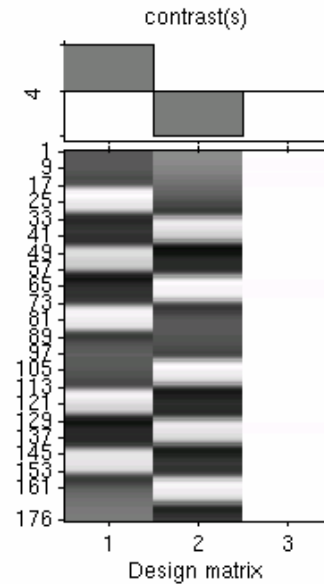
Convolved with HRF
gives the regressor



exp-con



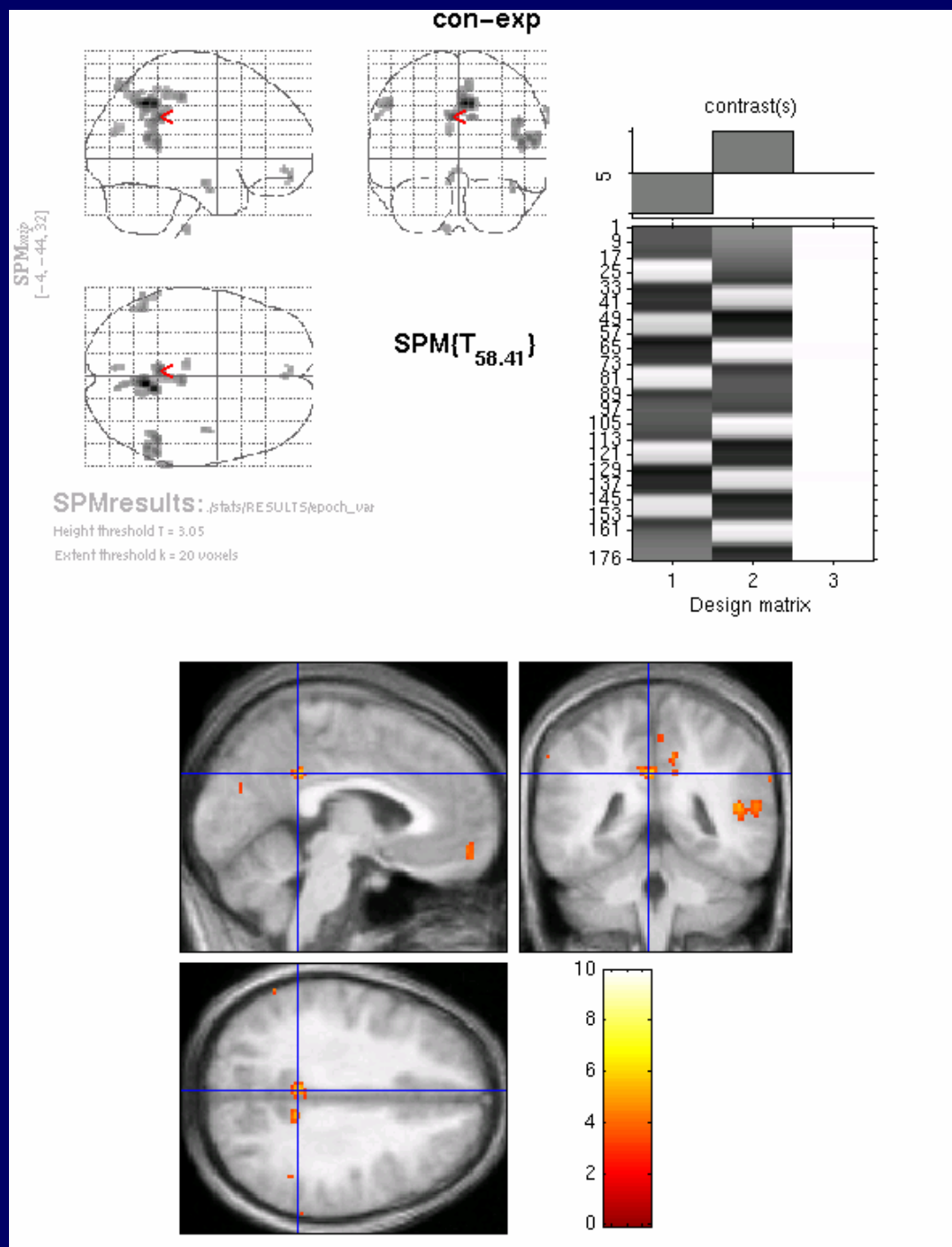
SPMresults: ./stats/RESULTS/epoch_var
Height threshold $T = 3.24$
Extent threshold $k = 25$ voxels



Single subject activation
during a verbal
encoding task

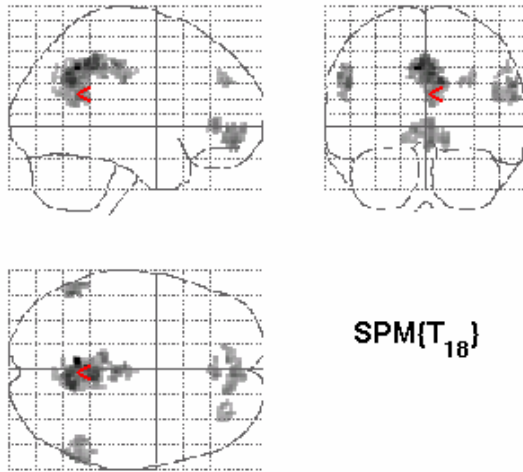
Deactivation

- Activation occurs in regions where BOLD signal is greater during experimental epochs versus control or rest epochs
- Deactivation occurs in regions where BOLD signal is greater during rest or control epochs versus experimental epochs



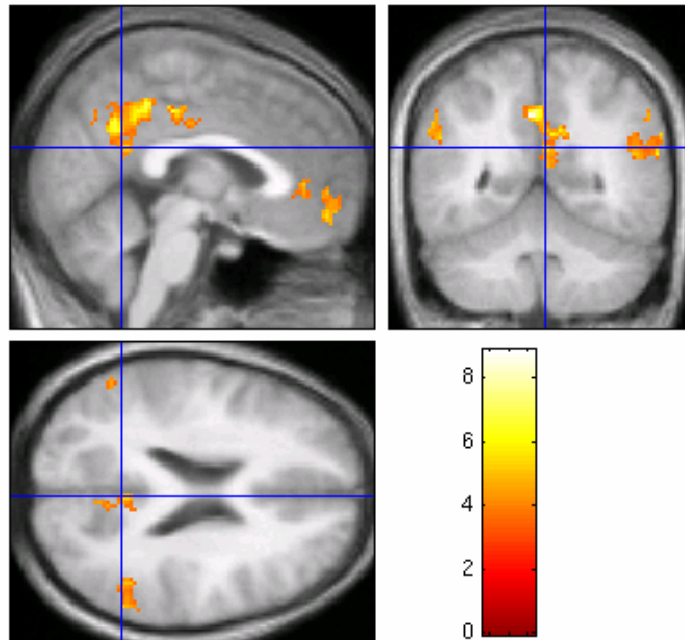
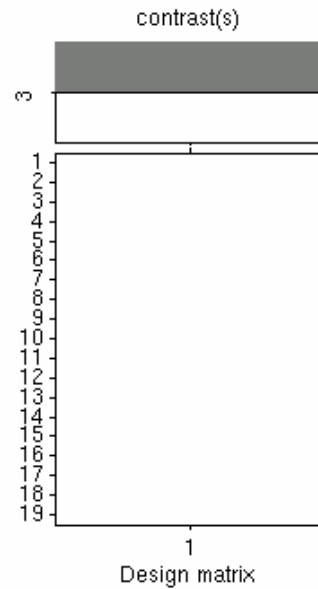
Single subject deactivation
during a verbal
encoding task

SPM_{display}
[2.78698, -54, 22.7417]



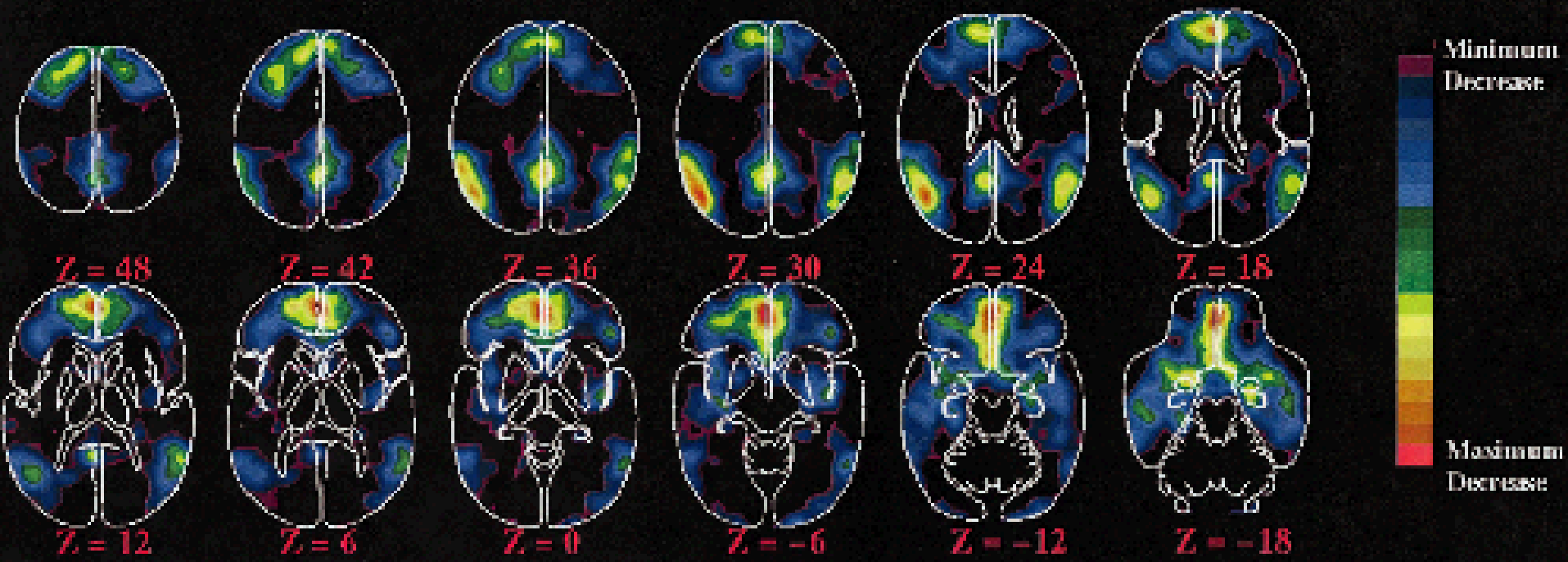
SPM $\{T_{18}\}$

SPMresults: .pmd_encoding_pre\group19
Height threshold $T = 3.61$
Extent threshold $k = 25$ voxels



Group level deactivation
in a verbal encoding task

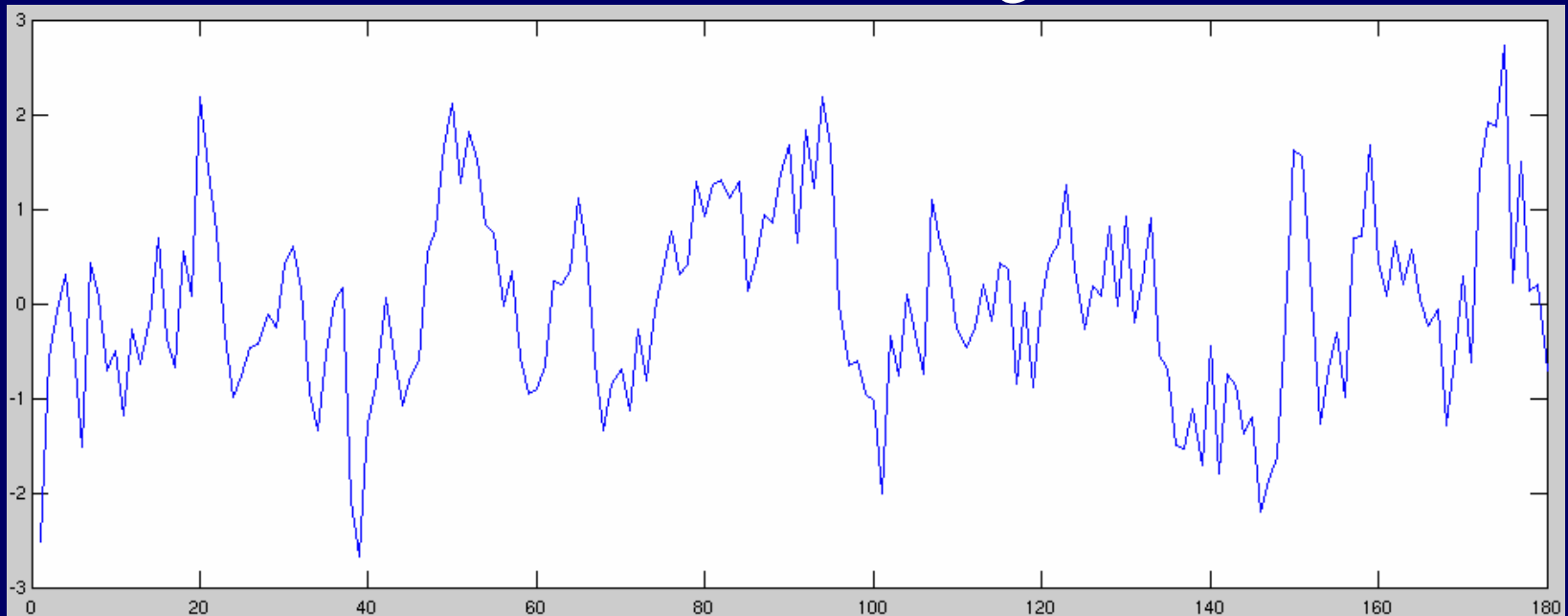
Deactivation, Resting Metabolism, and the Default Mode of Brain Activity



Raichle et al., *PNAS*, 2001

Resting-State Functional Connectivity

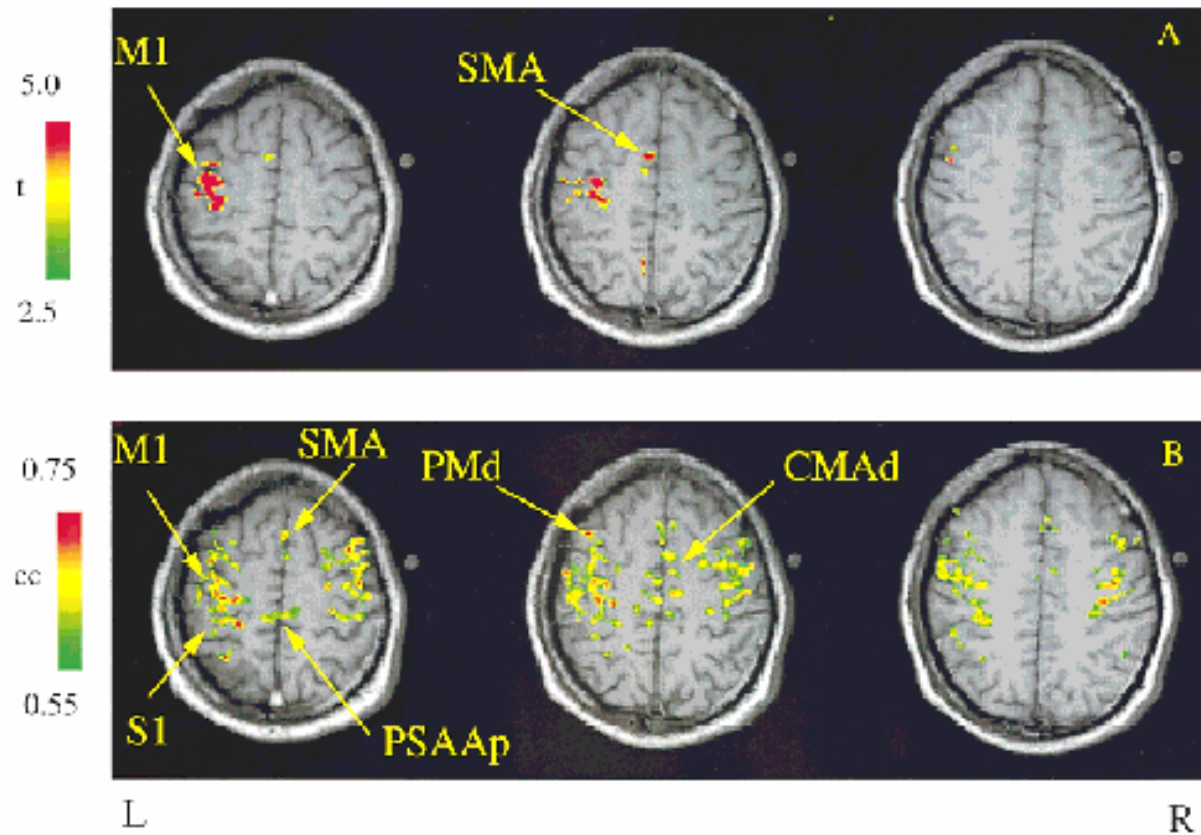
- Brain activity continues in the absence of an externally-cued task
- Any brain region will therefore have spontaneous fluctuations in BOLD signal
- A brain region's “resting” BOLD signal timecourse can be used as the regressor



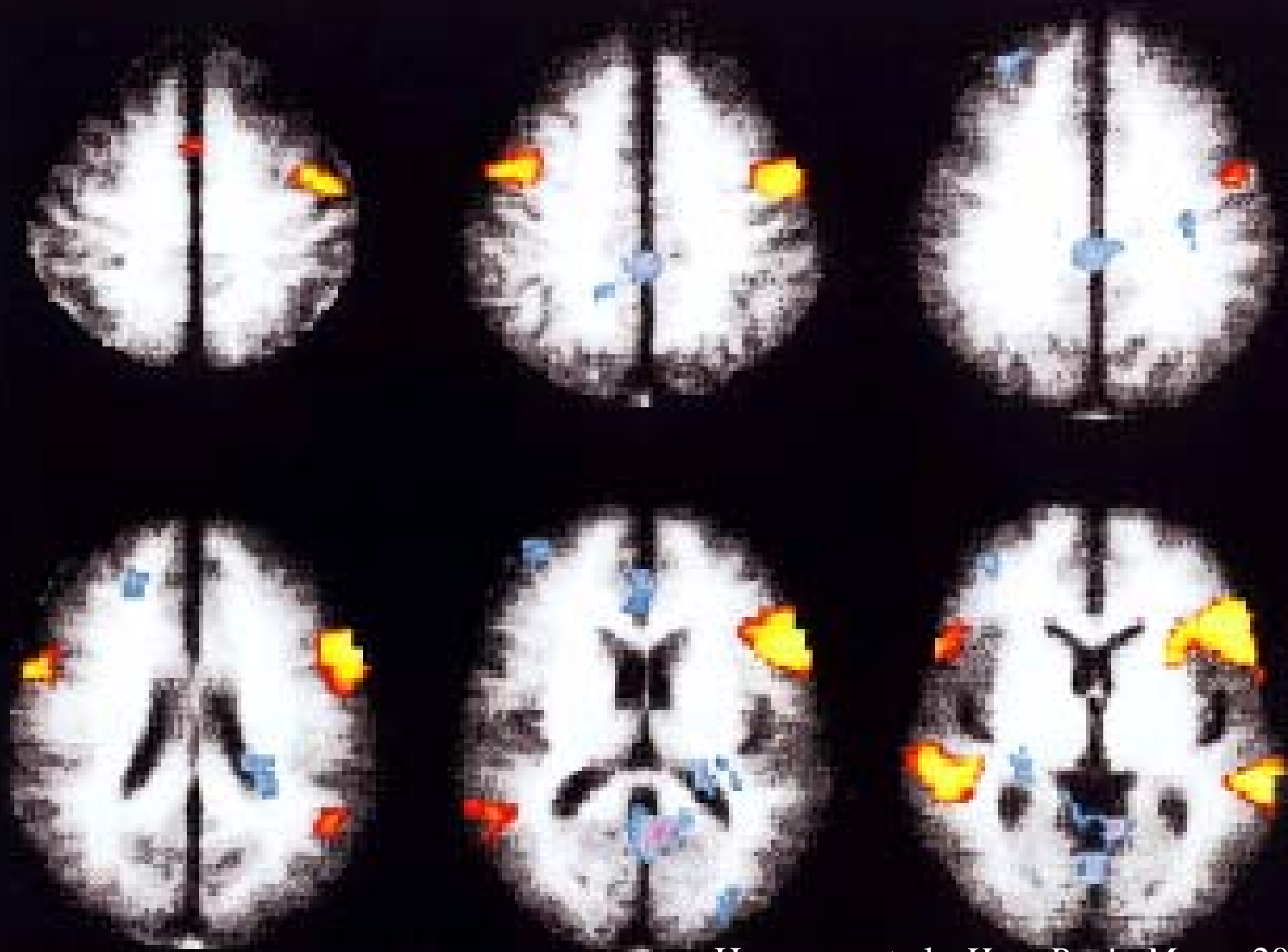
Resting-State continued

- Biswal et al., 1995 generated resting-state maps of motor cortex
- Roughly 30 papers since looking initially at sensory and motor cortices, more recently at cognitive regions.

= Resting-state Interregional Connectivity =

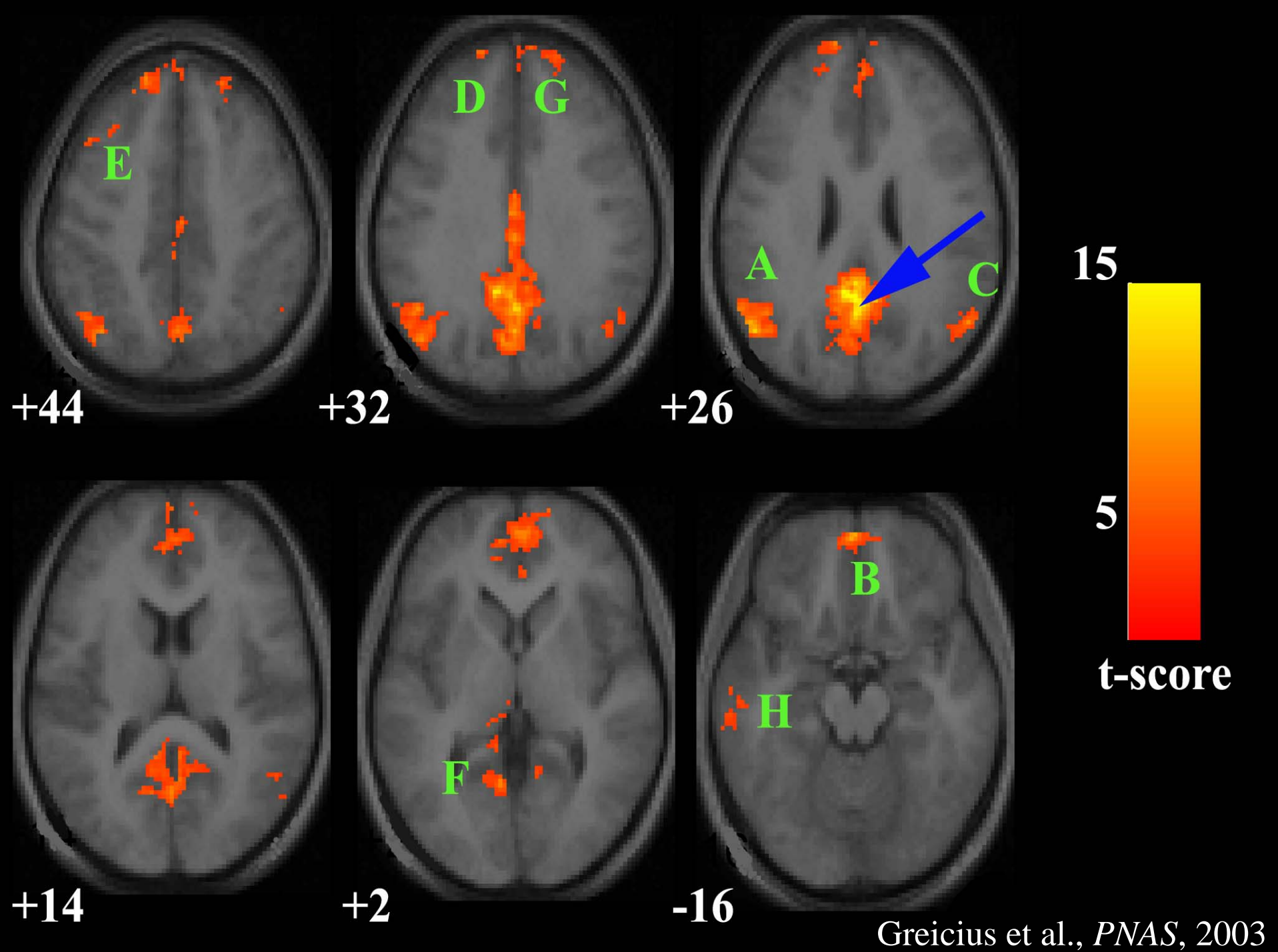


Xiong et al., *Hum Brain Mapp*, 1999

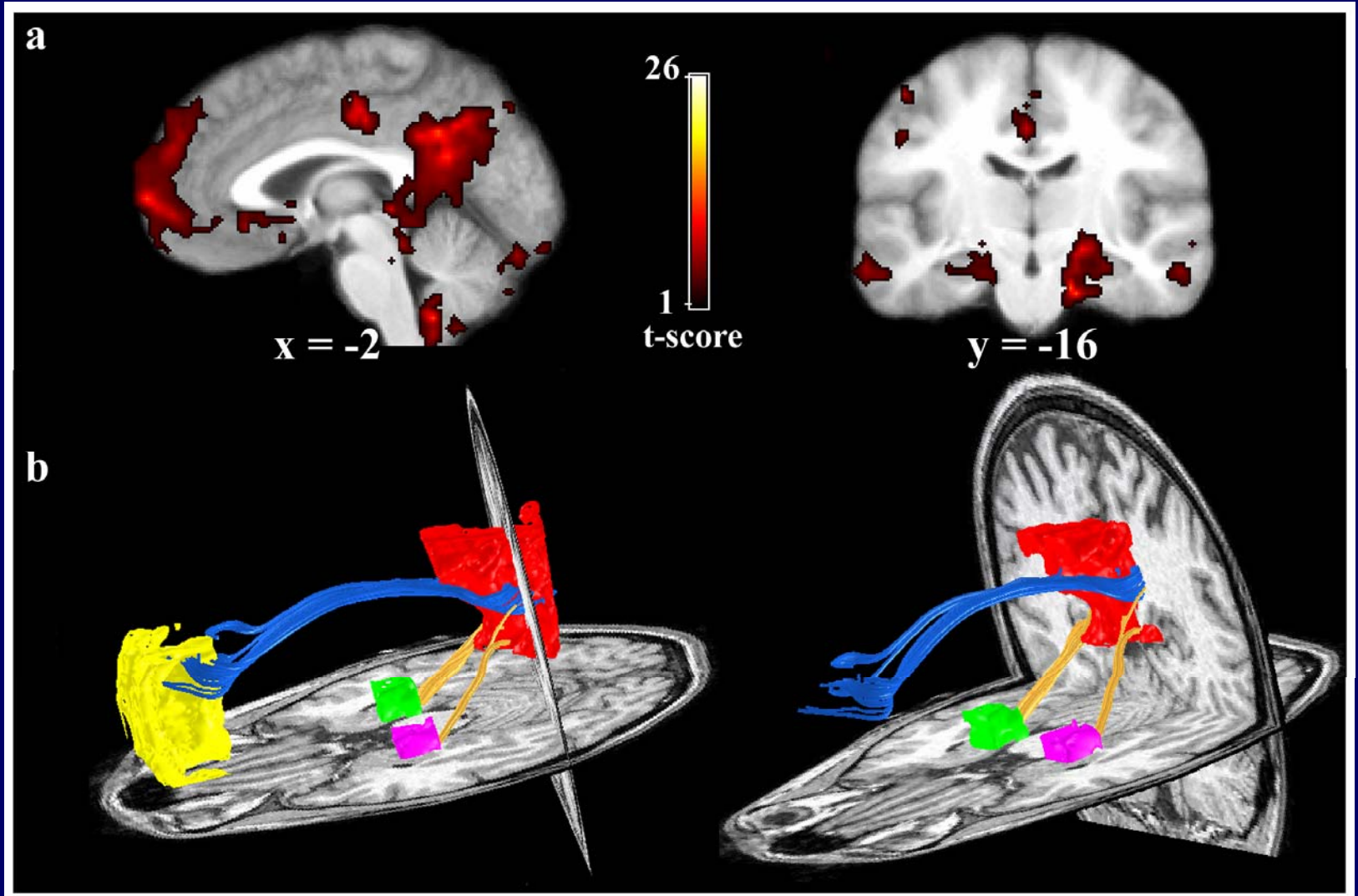


Testing the Default-Mode Hypothesis with Resting-State Functional Connectivity

- Defined deactivated region in the posterior cingulate cortex during a working memory task
- In a separate scan during 4 minutes of rest used the posterior cingulate timeseries as a regressor and derived a resting-state connectivity map



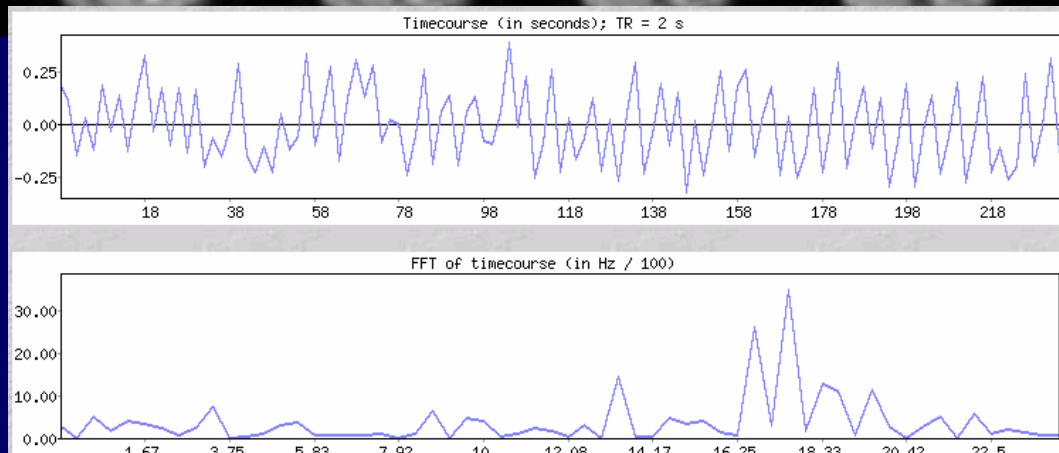
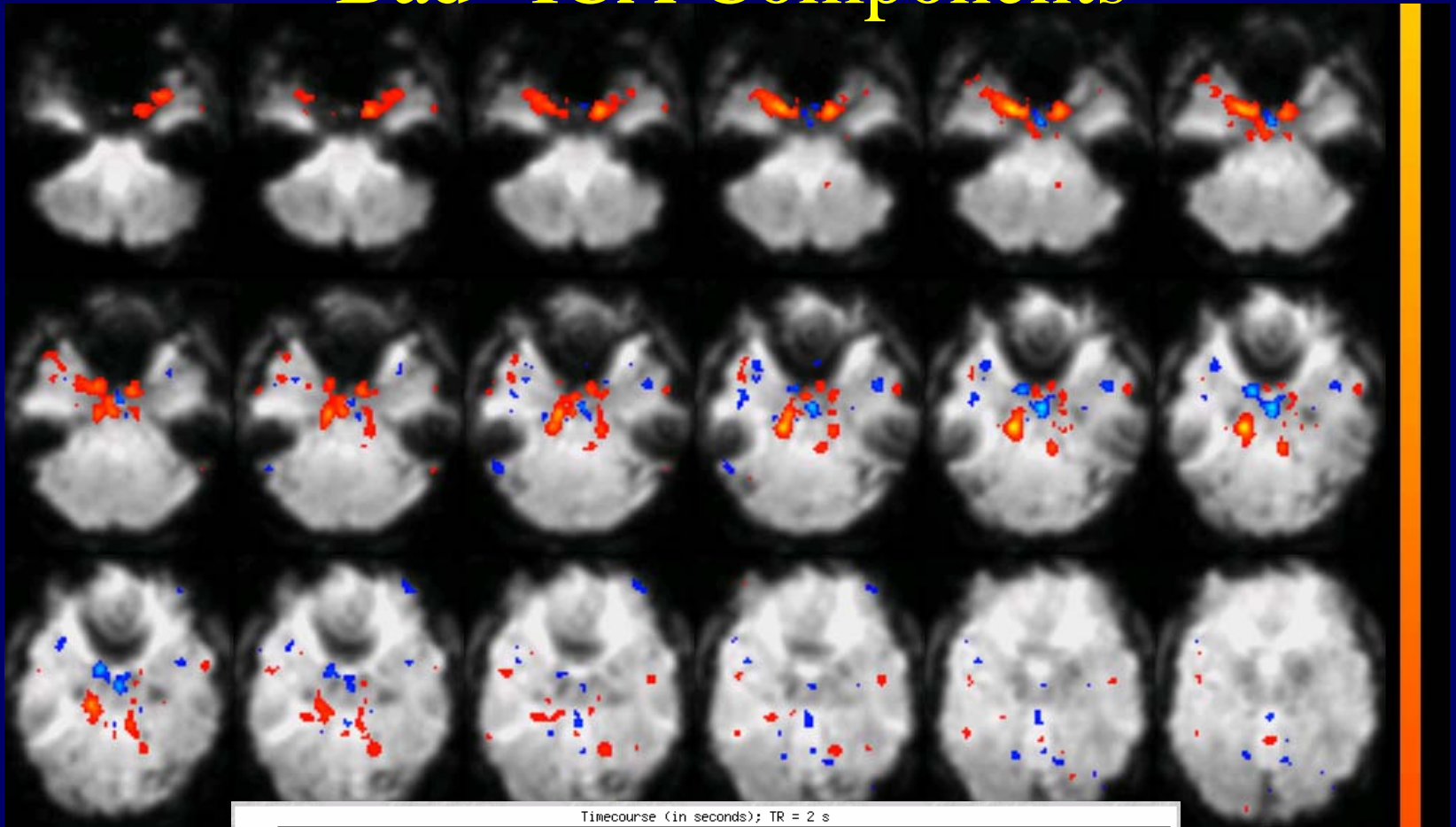
Functional Connectivity Reflects Structural Connectivity

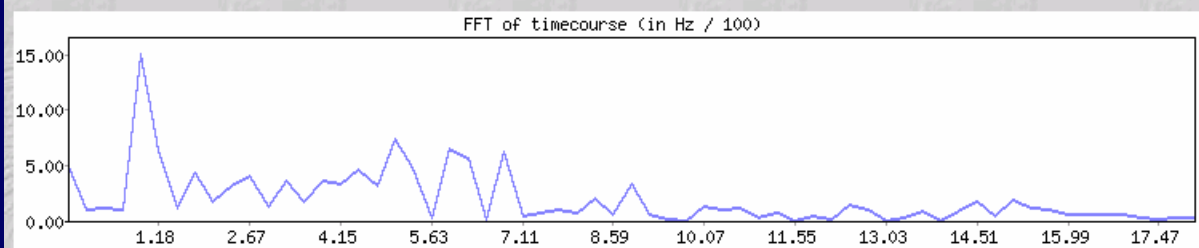
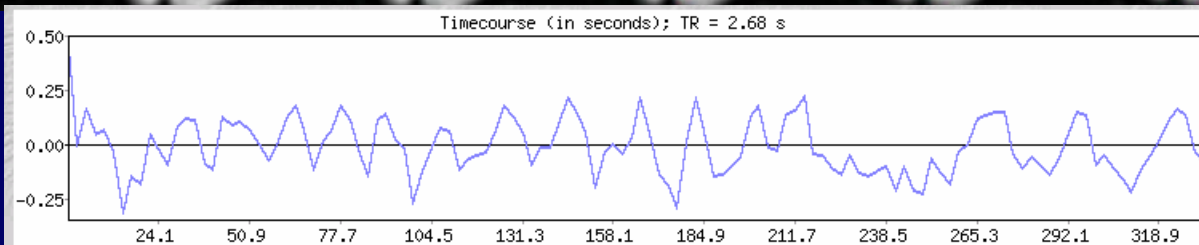
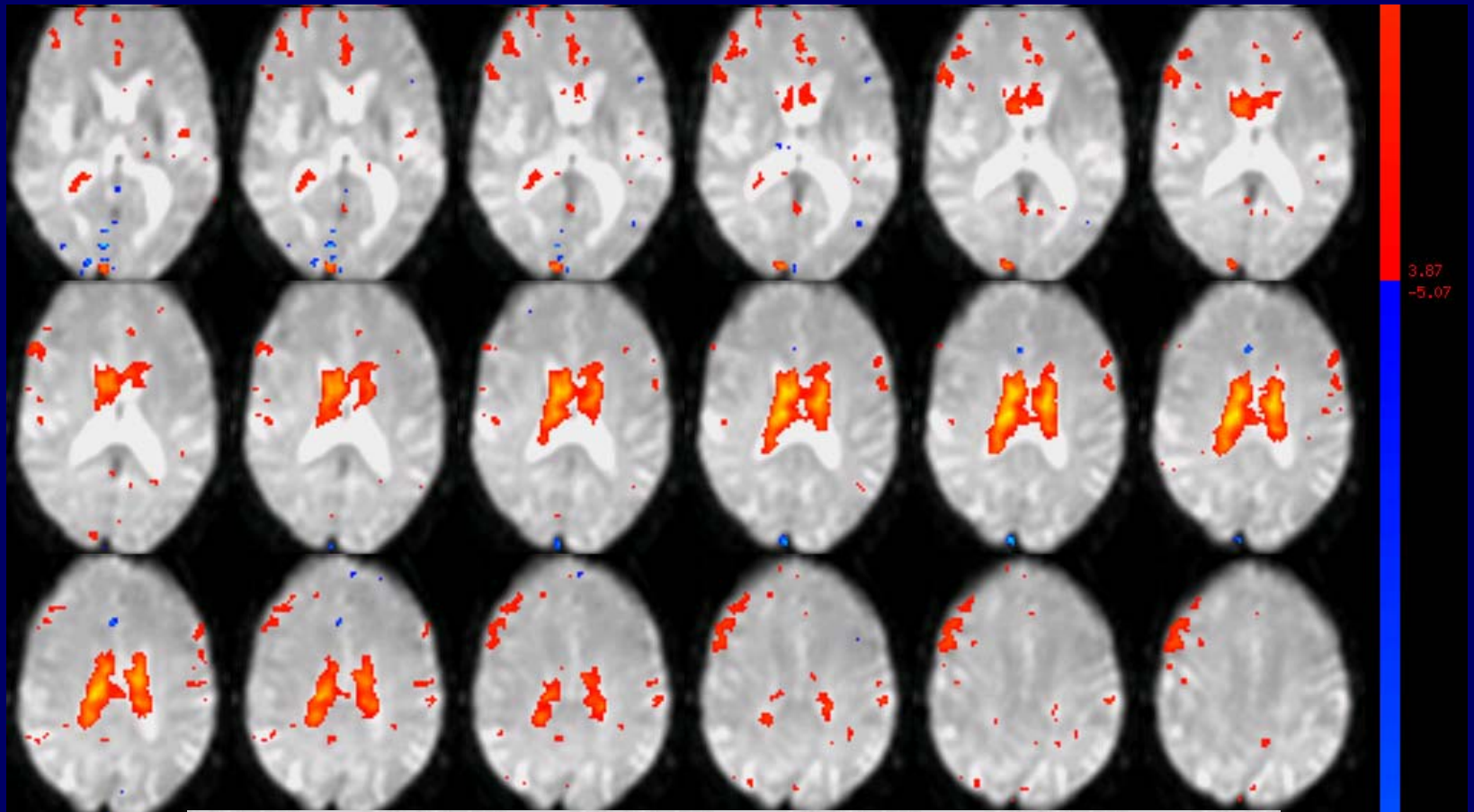


Independent Component Analysis in the Detection of Resting-State Networks

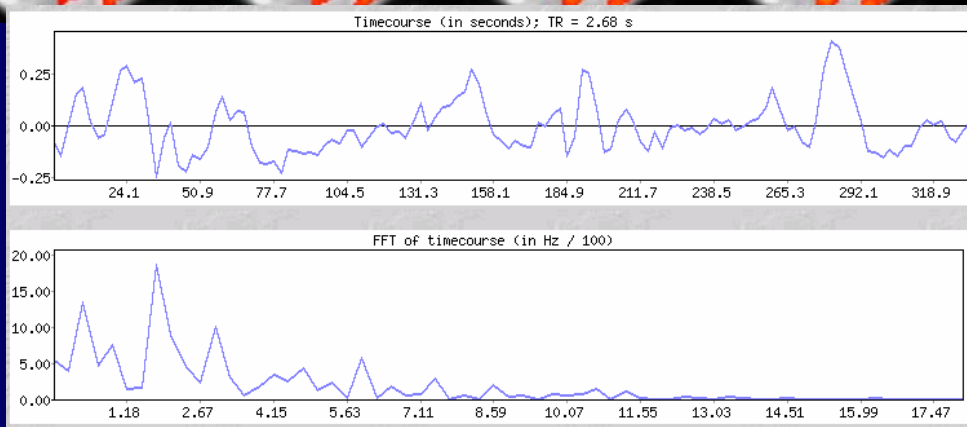
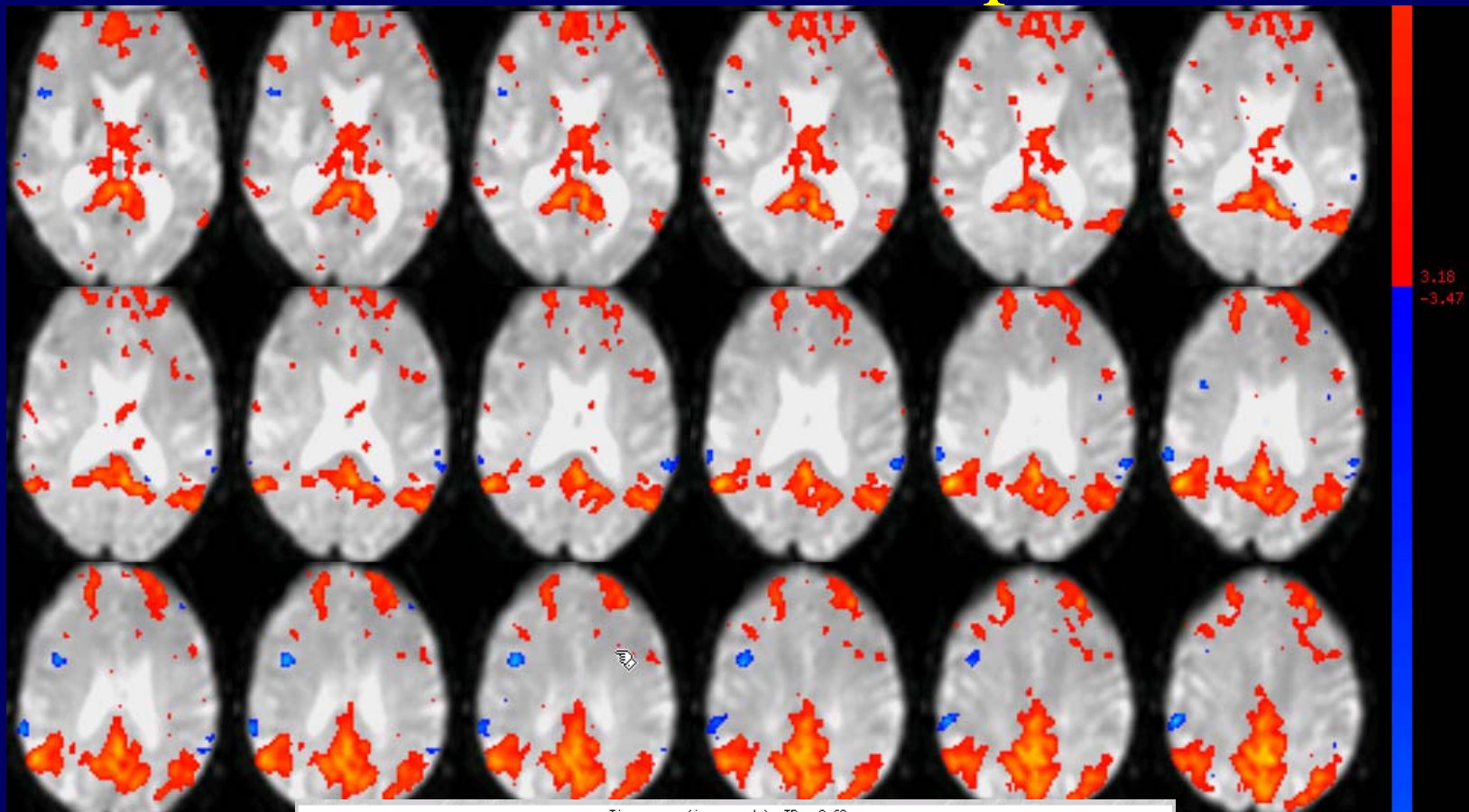
- ICA separates a signal (such as T2* signal of fMRI) into non-overlapping spatiotemporal components
- Data-driven
- Allows for better removal of noisy components (motion, scanner drift, etc).
- Reliably extracts default-mode network (and others) en bloc

“Bad” ICA Components

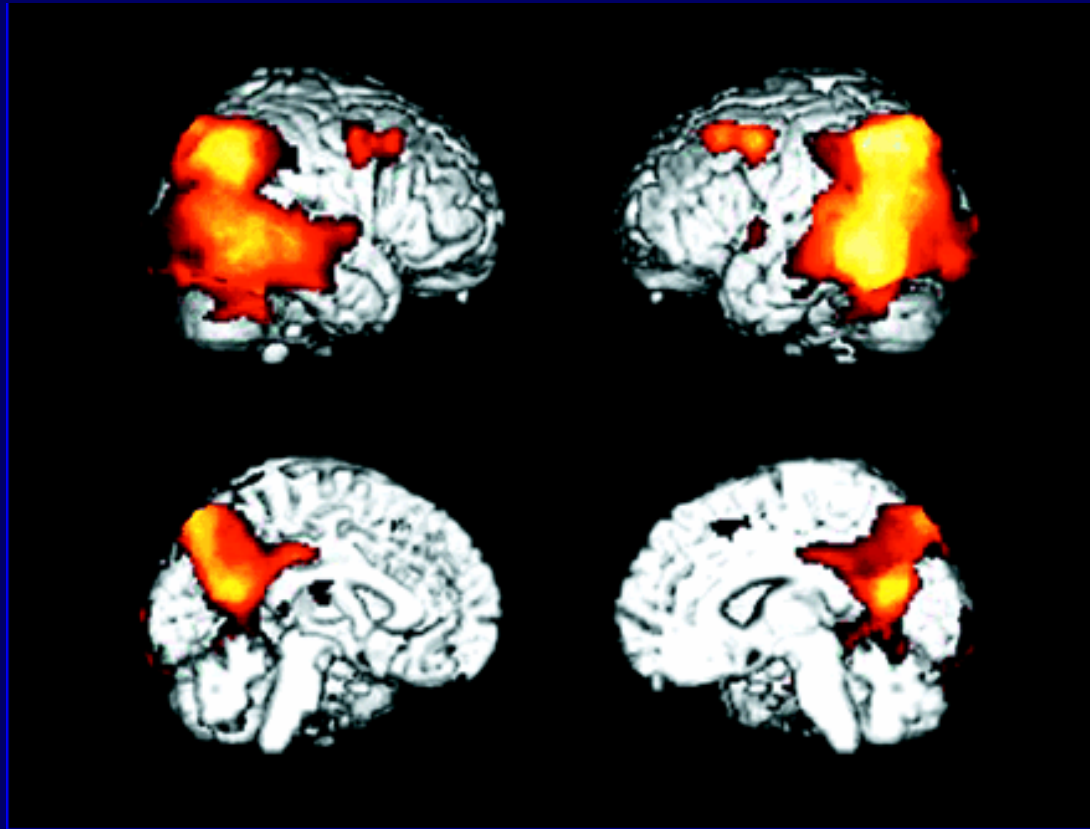




“Good” ICA Component



Hypometabolism in AD



Resting PET 34 healthy subjects versus 14 AD patients.

Alexander et al., *Am J Psychiatry*, 2002.

Default-Mode Network in Alzheimer's Disease

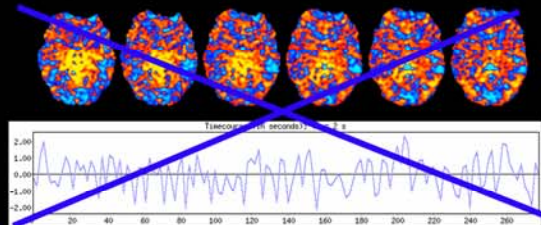
- Dataset #2-2000-1118W from the fMRI Data Center (Buckner and colleagues)
- Healthy young, healthy aging, and very mild AD in a simple sensory-motor task
- ICA to extract default-mode network in each subject (using our healthy young subjects' network as template)
- Median image calculated from 4 runs/subject

Automated Detection of the Default-Mode Network

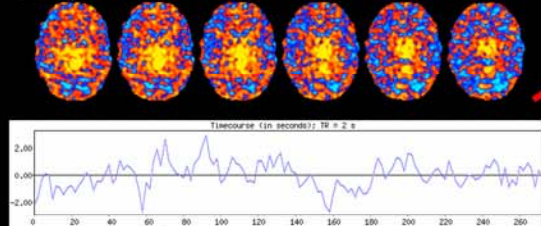
Step 1: High frequency components removed with frequency filter.

Step 2: Remaining low frequency components scored on goodness-of-fit to standard template.

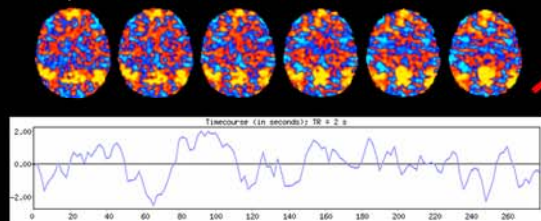
Component 1



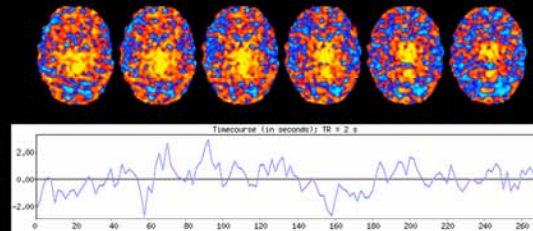
Component 2



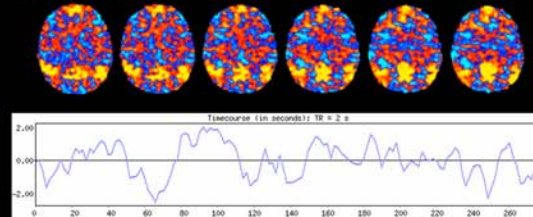
Component 3



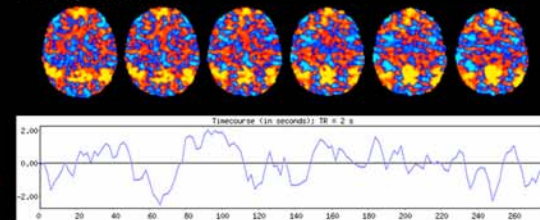
Component 2



Component 3

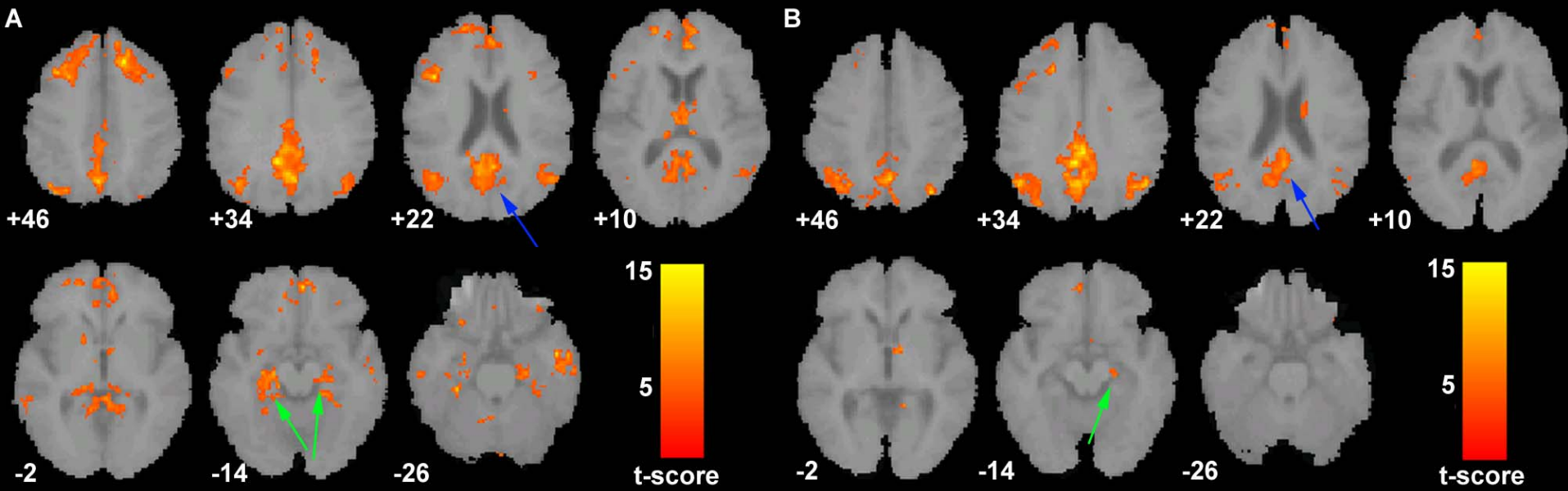


Component 3



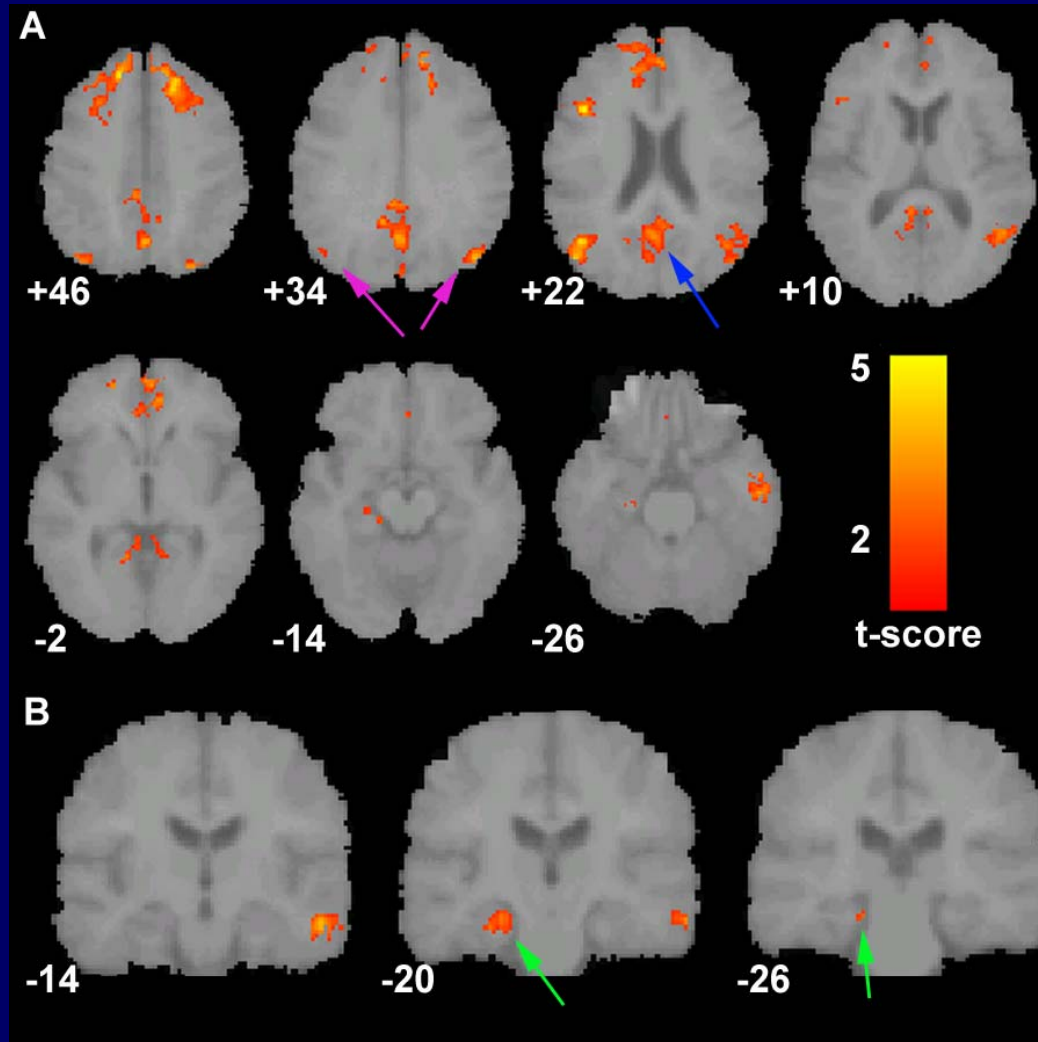
Component with highest goodness-of-fit score selected as default-mode component to be used in group analyses.

Default-Mode Network in AD



ICA-based detection of default-mode network in healthy aging (A) and AD (B).

Default-mode in healthy aging versus AD



Oedipal Interlude/ Single-Subject Feasibility

PLAYING

MOM

DAD

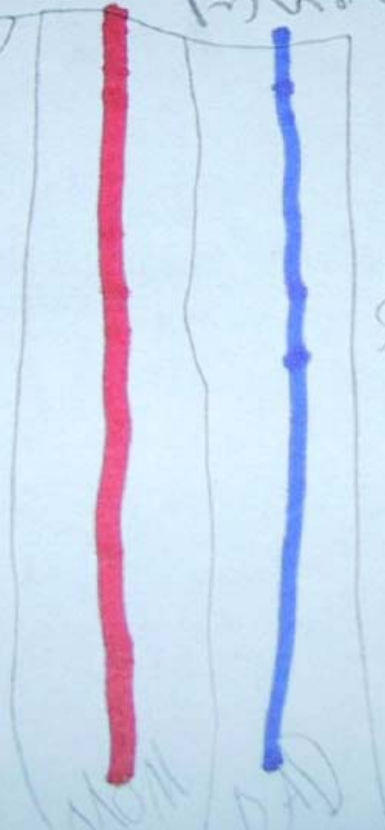
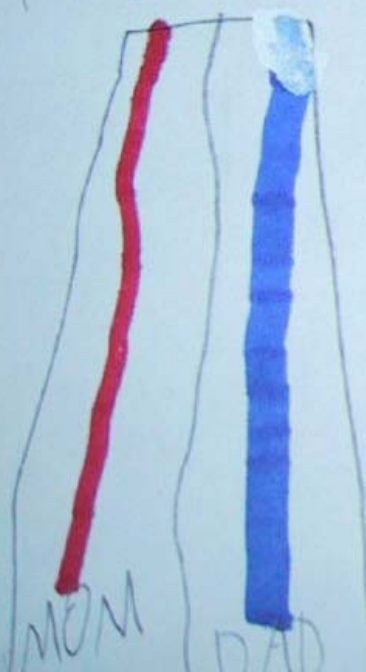
MOM AND DAD GRASP

PROMISE READING

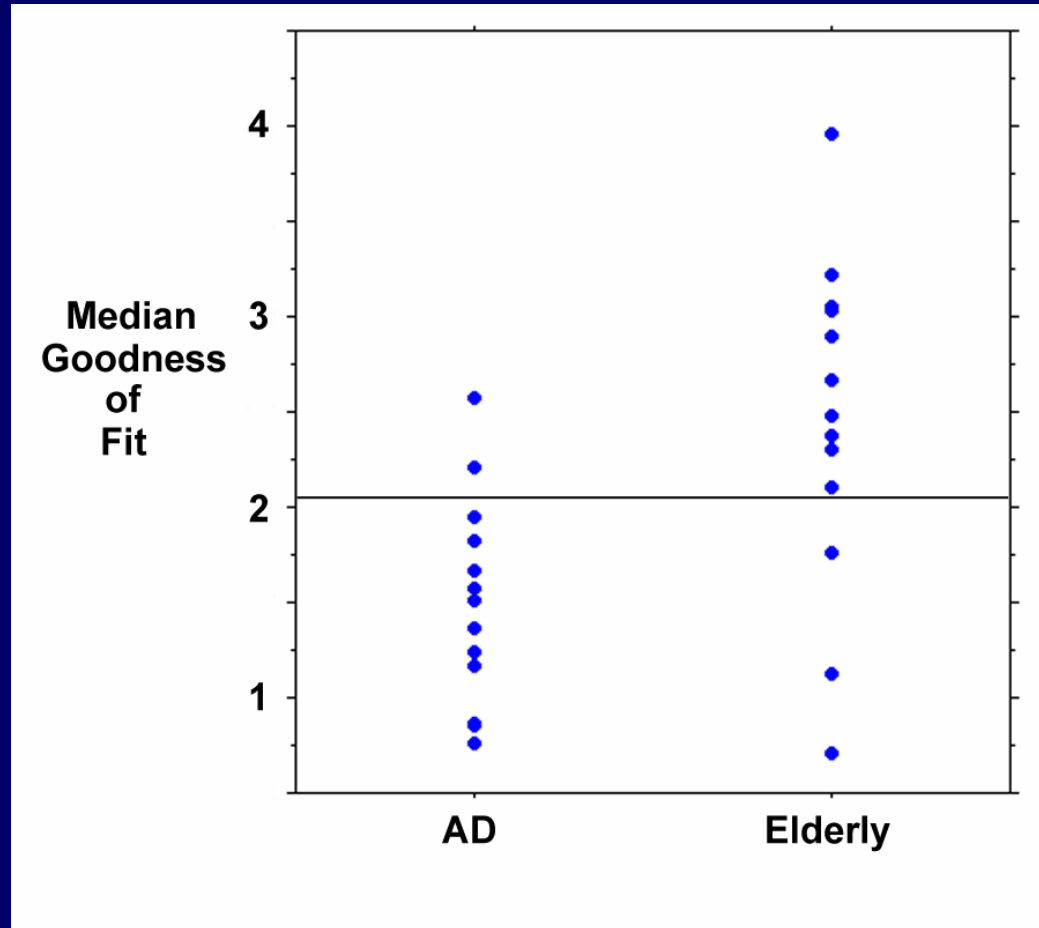
manbad = I

LOVEING

SKETCH

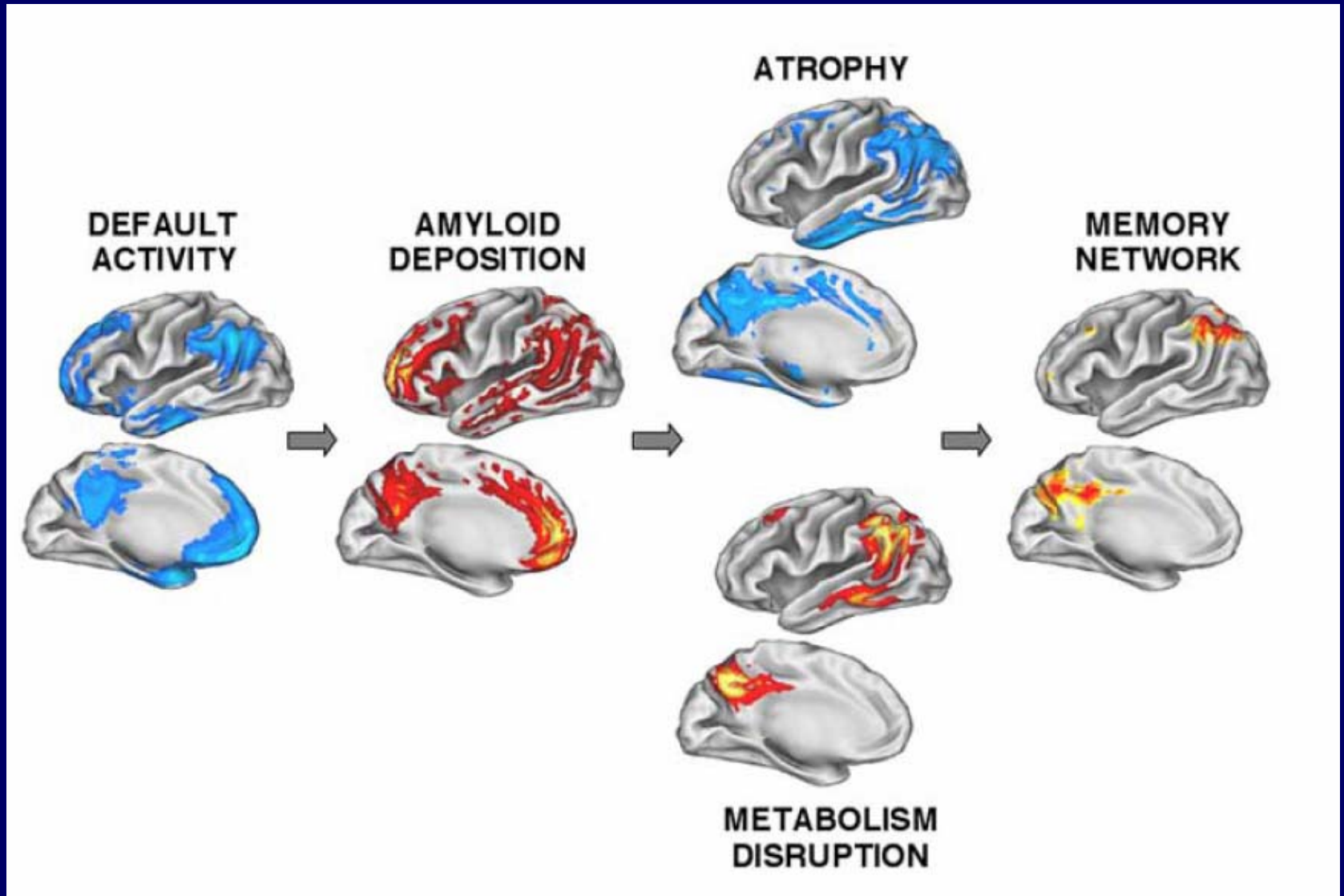


Goodness of Fit to Healthy Young Default-Mode Network



Two-sample t-test ($p = 0.003$). Mann-Whitney test ($p = 0.007$).
85% sensitivity and 77% specificity with 2.1 as the cutoff

All Roads Lead to the DMN



Davis/Stanford MCI Study

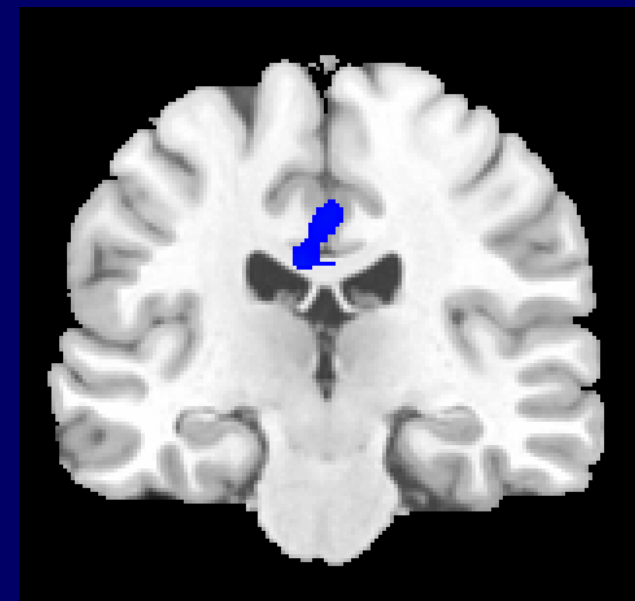
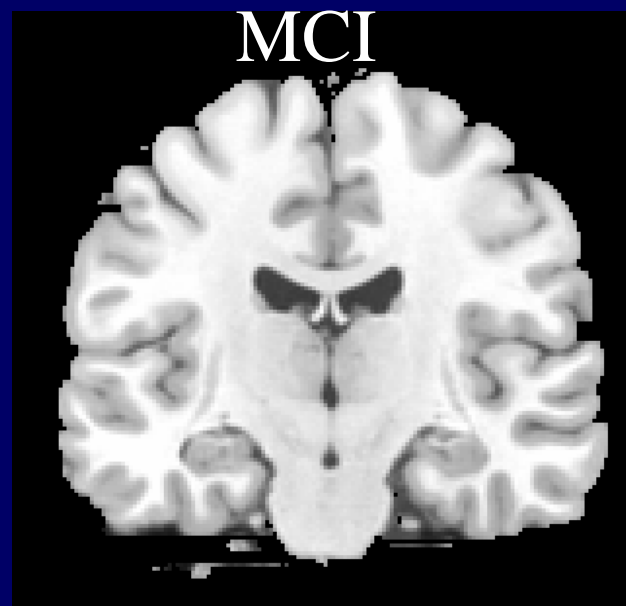
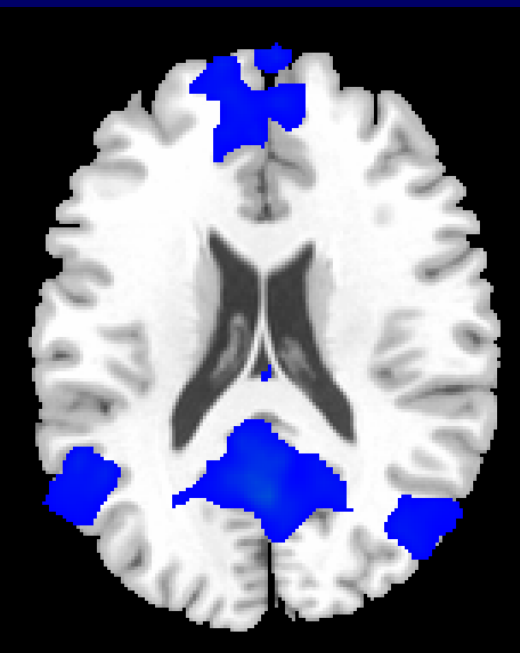
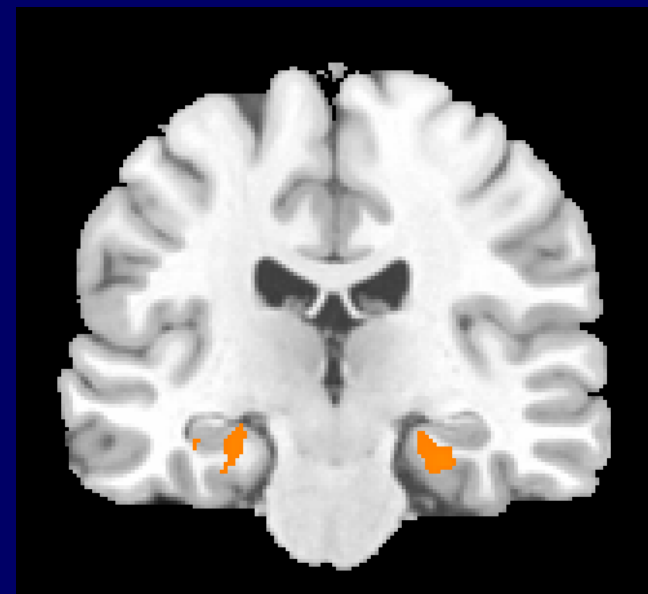
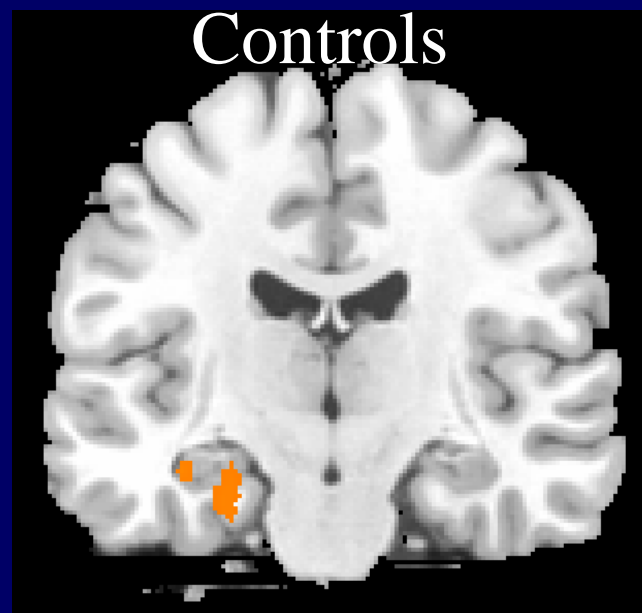
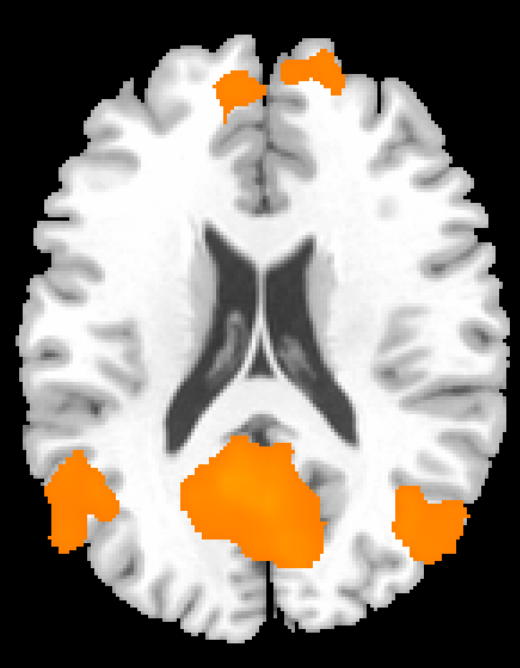
Methods

- **Subjects**

	<u>9 MCIs (5 women)</u>	<u>9 controls (5 women)</u>
Age	75.2	74.8
Education	12.7	12.8
MMSE**	23.3	28.7

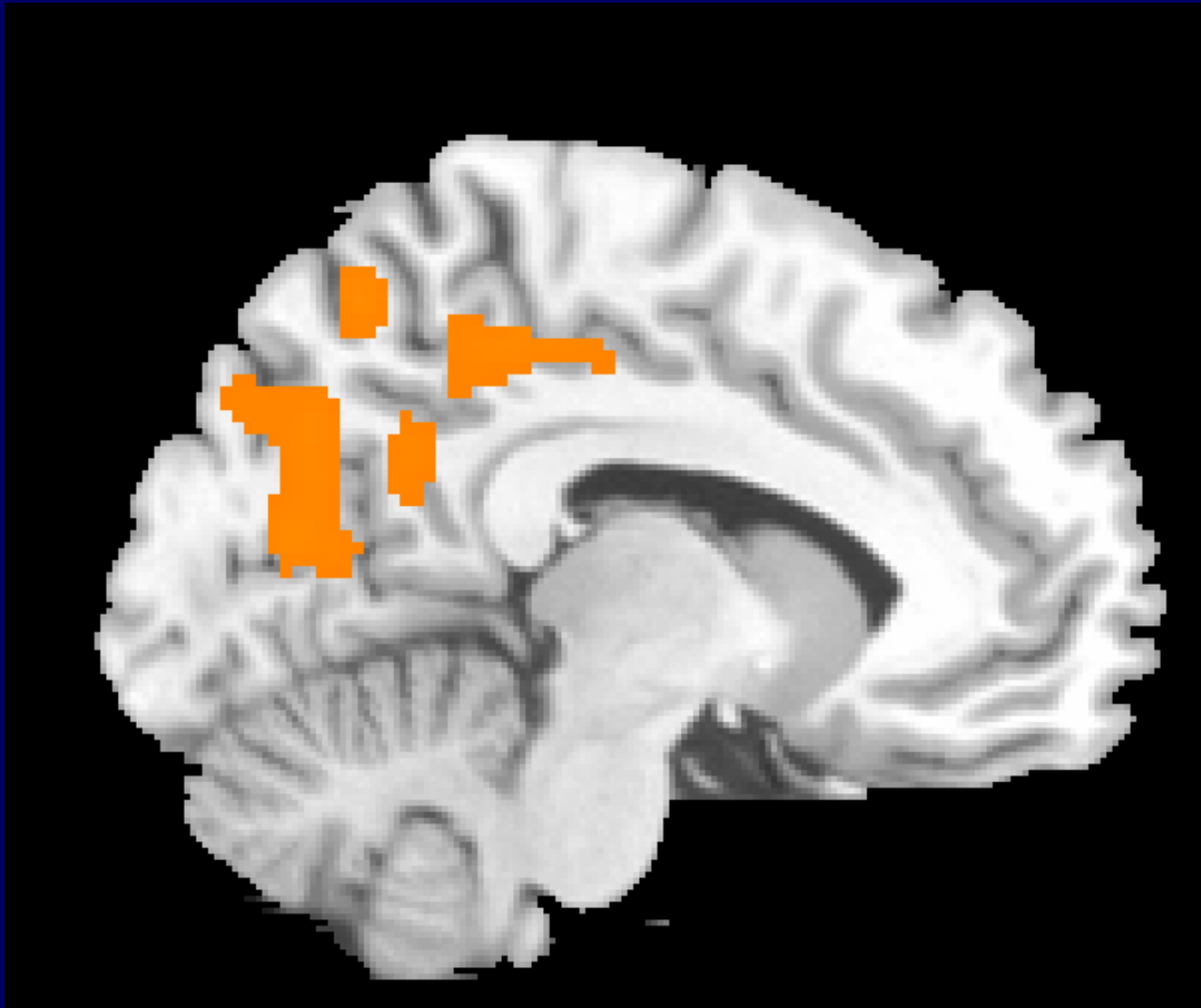
- **Scanning/Analysis**

- 8 minute resting-state fMRI scan
- 1.5 T, EPI sequence, 2 second TR (240 timepoints)
- SPM5 preprocessing, ICA with FSL's MELODIC



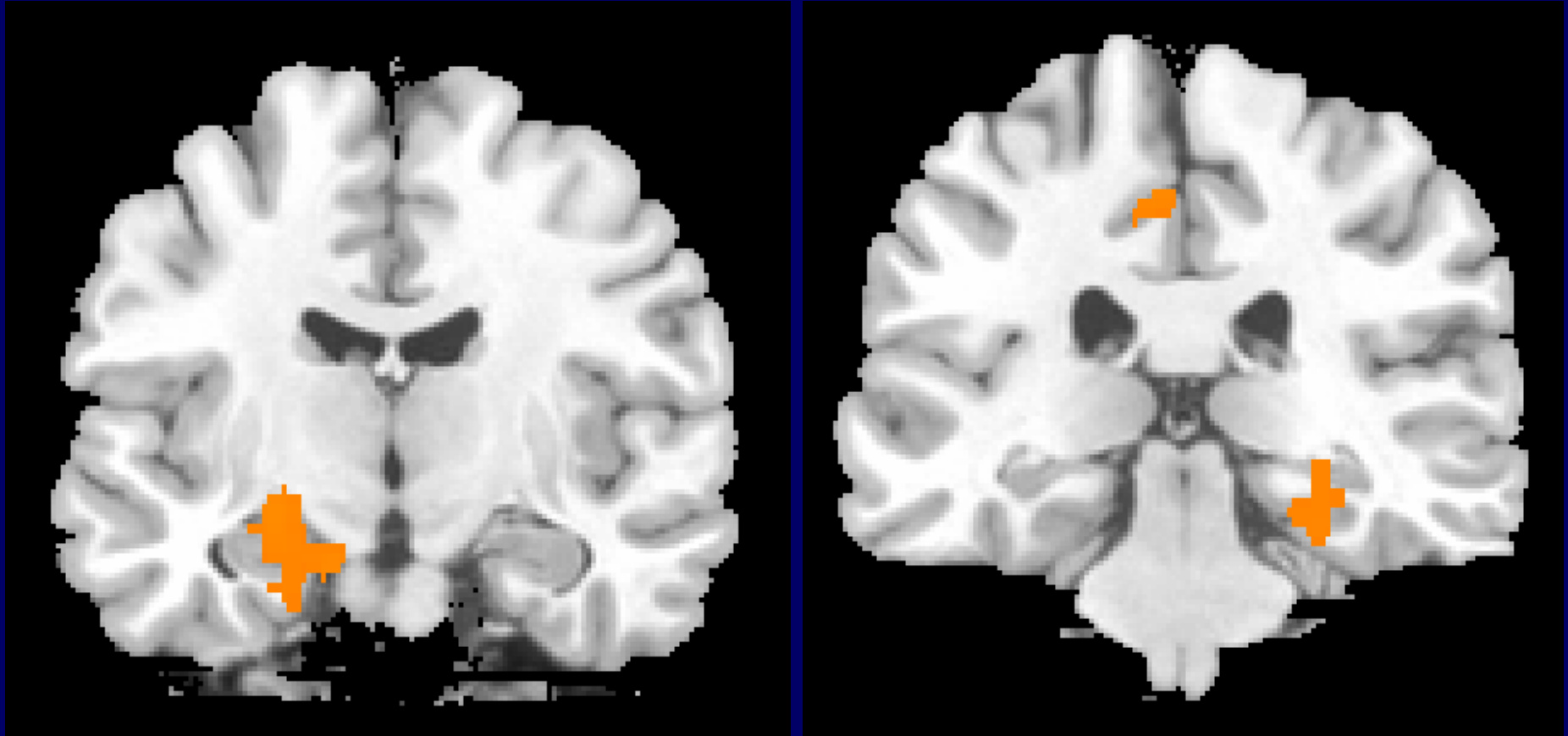
$p < 0.01$ (height and extent)

Control versus MCI



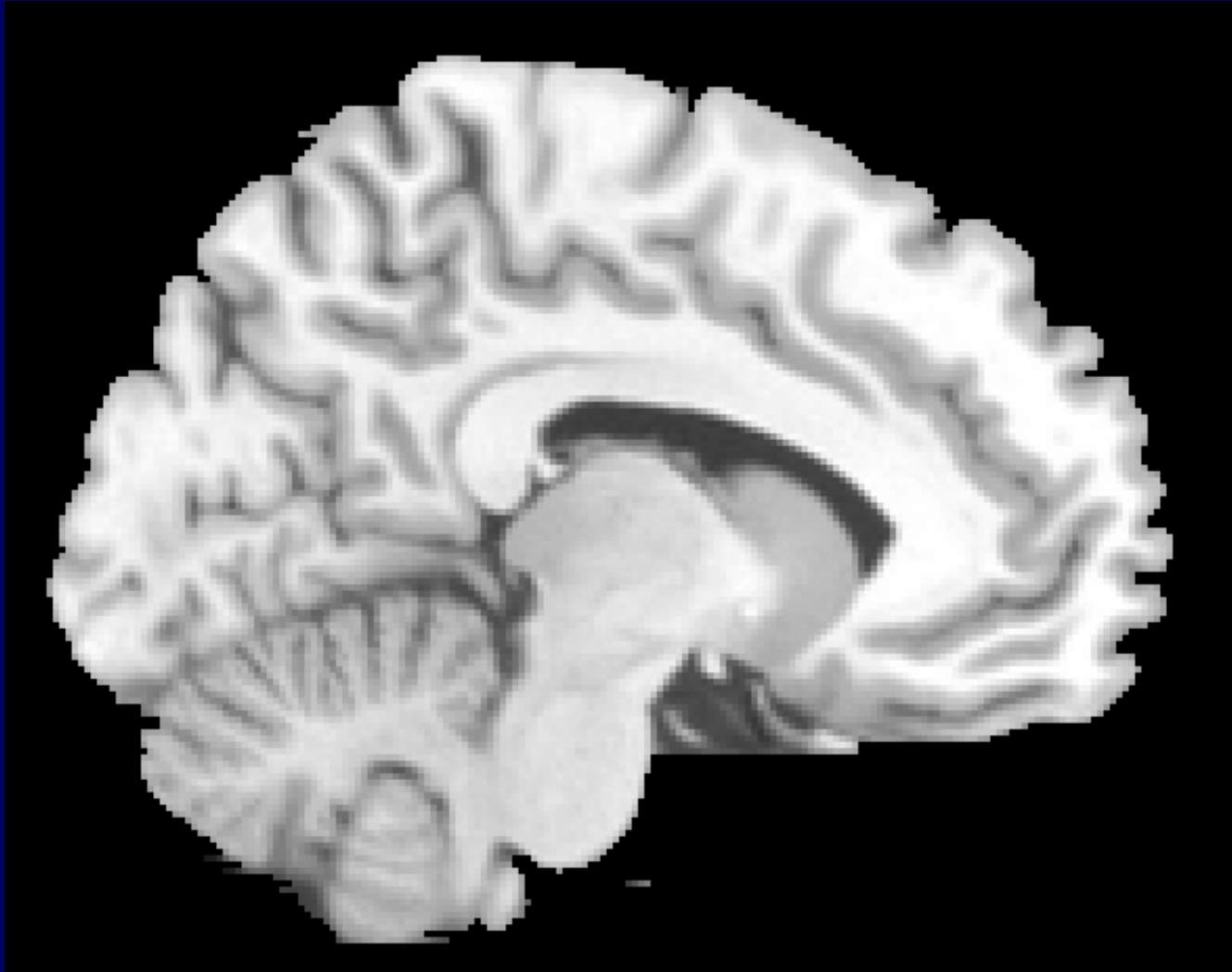
$p < 0.05$ (height and extent)

Control versus MCI

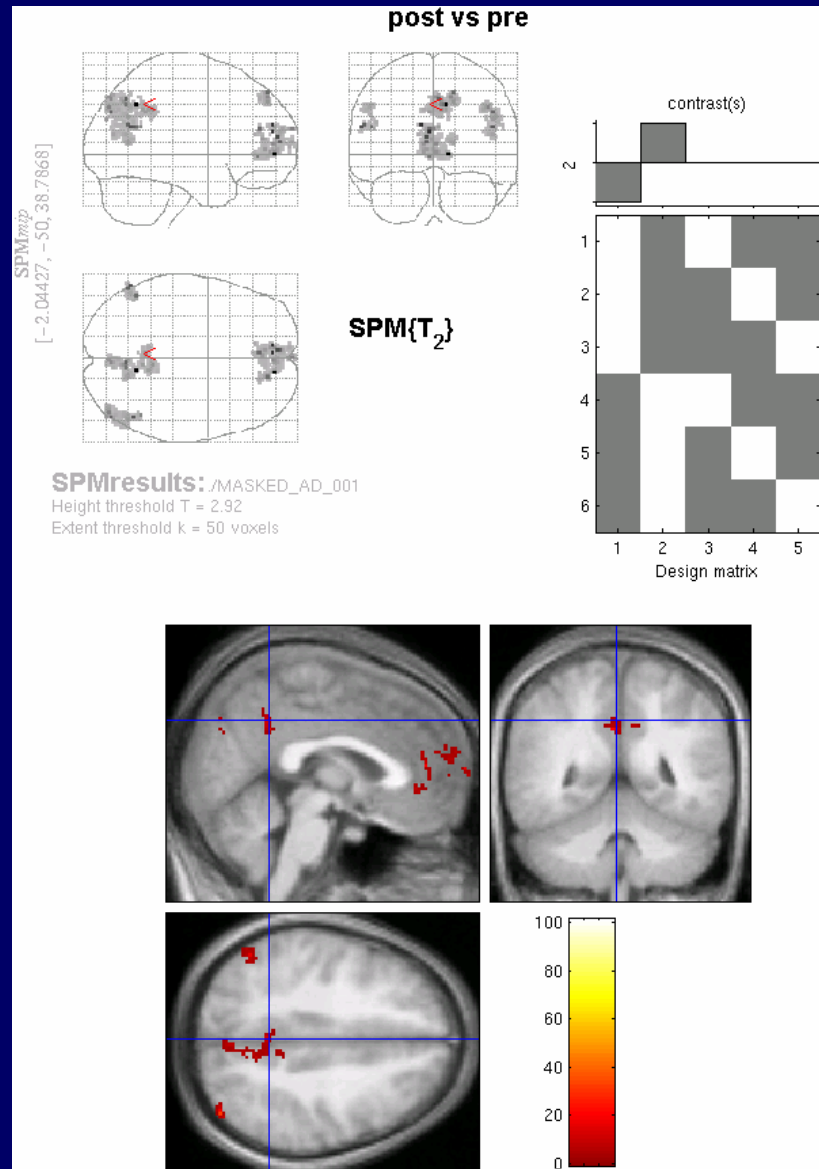


$p < 0.05$ (height, 200 voxel minimum cluster size)

MCI versus Control

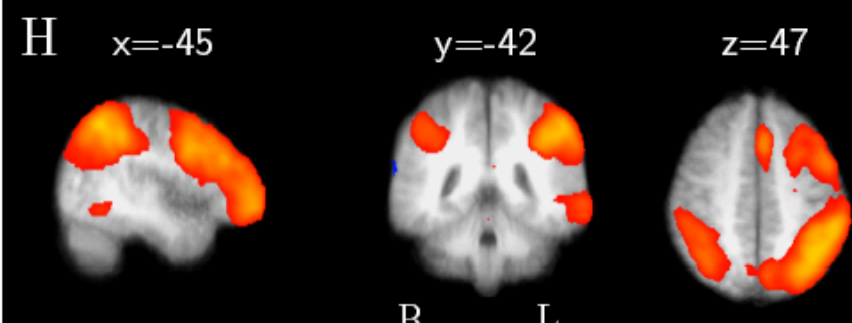
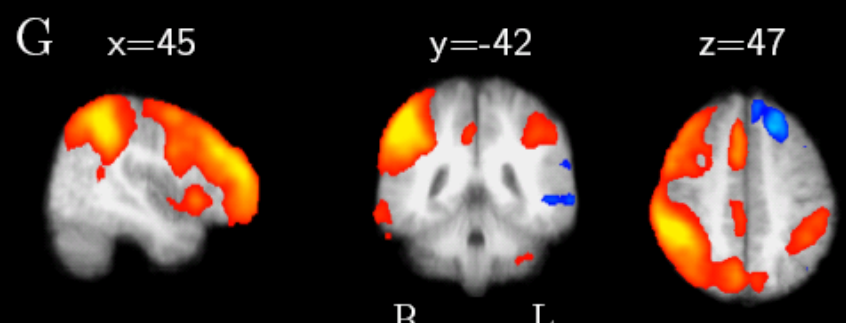
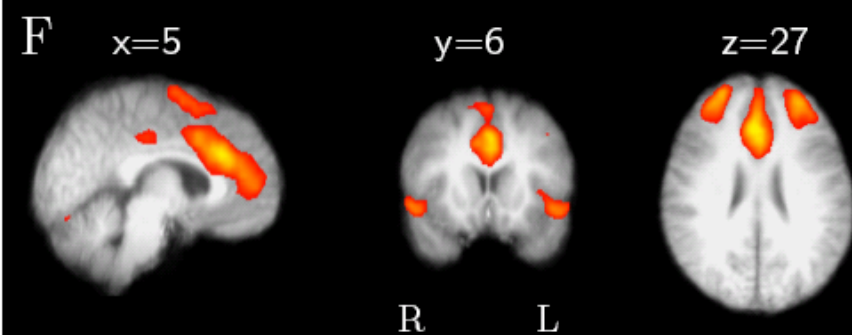
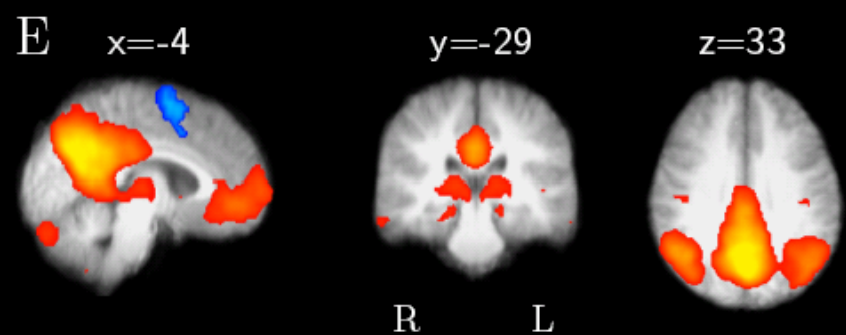
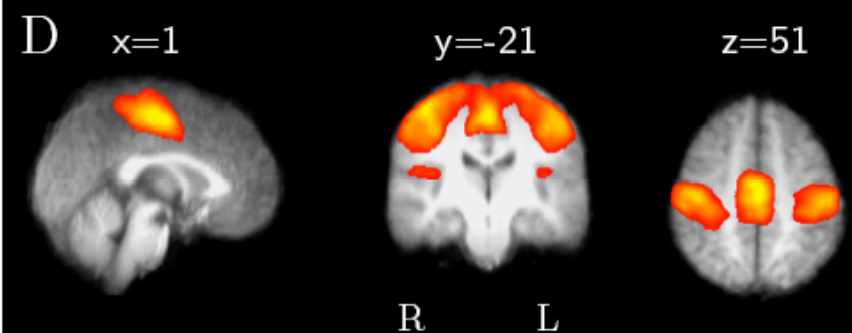
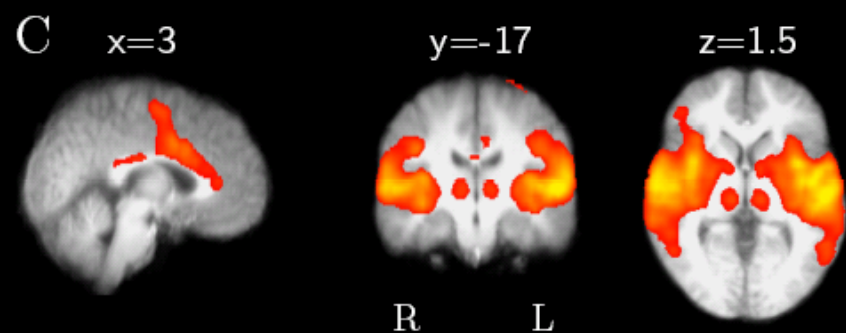
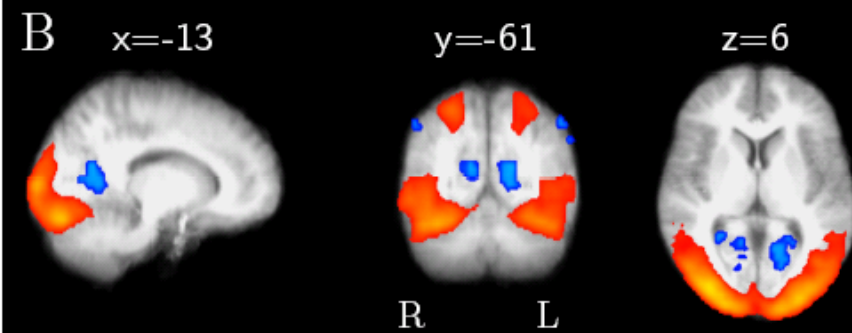
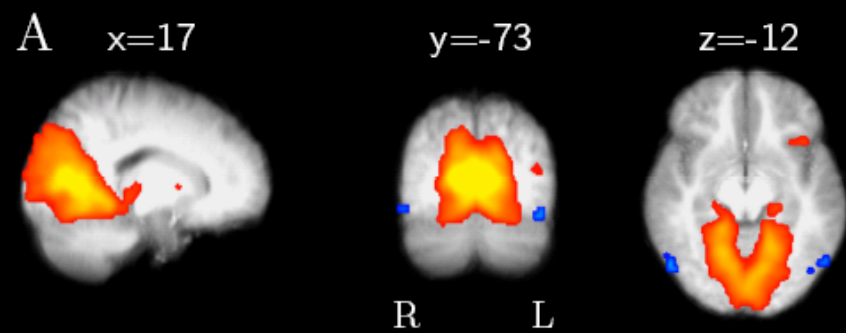


Early Marker of Treatment Efficacy



The Collected Resting-State Networks of Christian Beckmann

- Group ICA of 10 subjects during 10 minutes of rest
- Philos Trans R Soc Lond B Biol Sci. 2005 May 29;360(1457):1001-13.



Analysis of Resting-State Networks

- Several advantages over task-activation fMRI
- Easily and automatically done with ICA
- Potential clinical applications in Alzheimer's, and other neurodegenerative diseases

Collaborators

Stanford

Vinod Menon

Allan Reiss

Gary Glover

Kaustubh Supekar

Sean Mackey

Bob Dougherty

UCSF

Bruce Miller

Bill Seeley

UC Davis

Charlie DeCarli

Evan Fletcher

Oliver Martinez

Funding Support

The Alzheimer's Association: NIRG-04-1060

NIH: AG10129, AG021028, and NS048302

Special Thanks

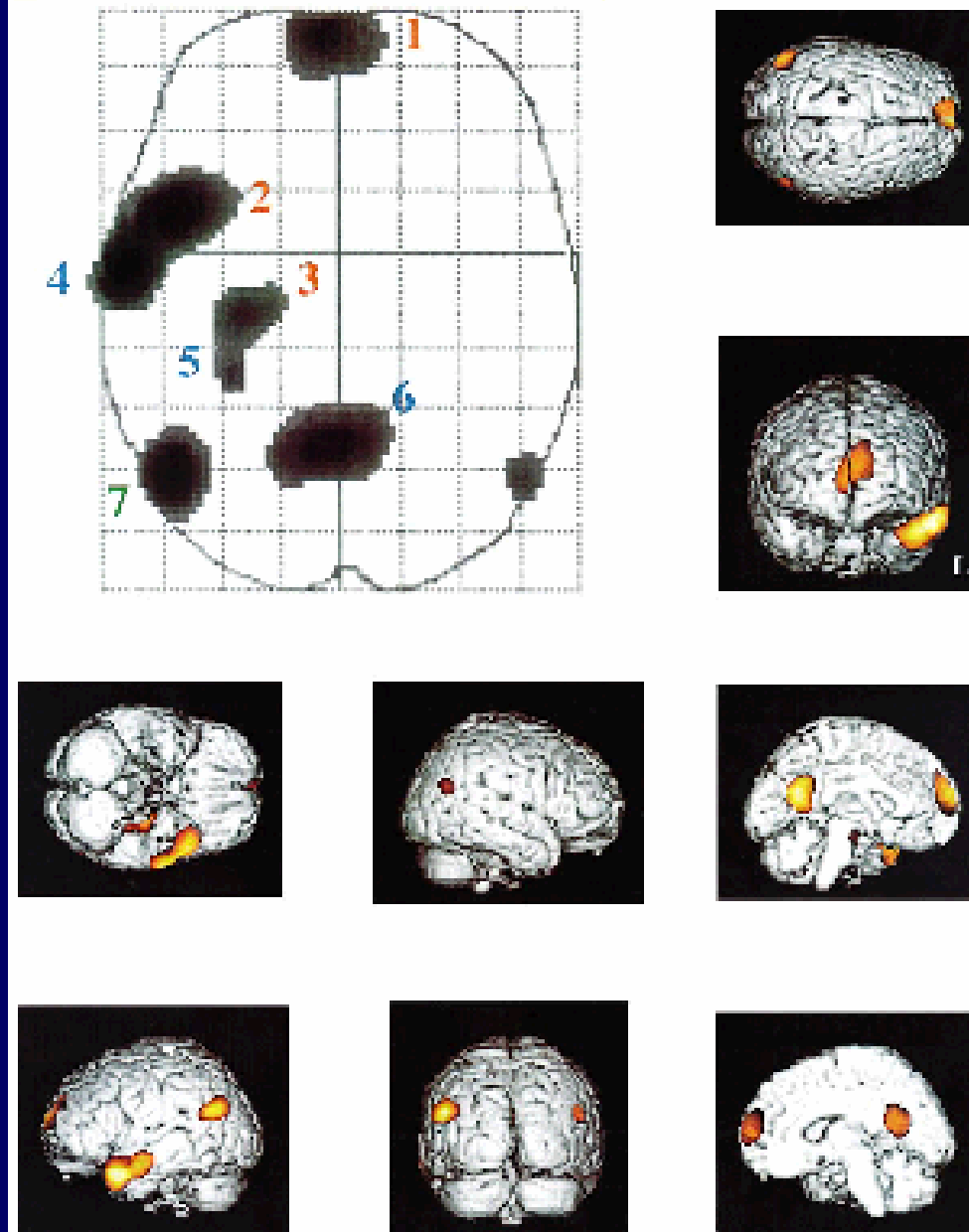
Christian Beckmann and the FSL group at Oxford

The fMRI Data Center www.fmridc.org

What Role Does the Default-Mode Network Play?

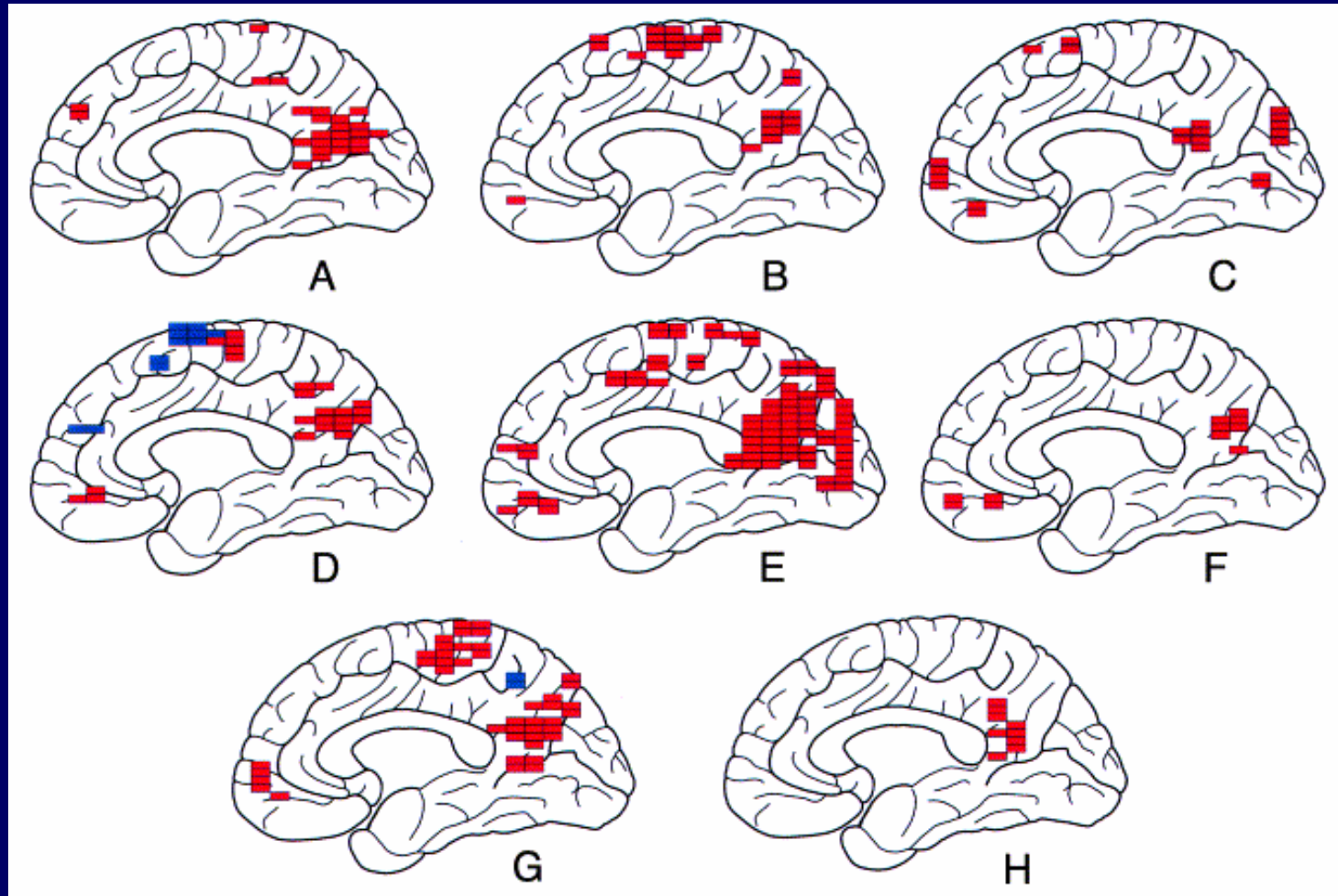
- Function is difficult, by definition, to assess directly with behavioral paradigms
- Rely instead on
 - lesion studies or lack thereof (Raichle's evolutionary theory)
 - task activation paradigms with default-modish activation maps
 - comparisons of network activity between two groups or states differing in some fundamental attribute
 - Interactions between the default mode and other networks

Episodic Memory Retrieval



Maguire and Mummery, *Hippocampus*, 1999

Posterior Cingulate and Autobiographical Memory



Maddock, Garrett, Buonocore, *Neuroscience*, 2001

Self-Appraisal (vs Semantic Decision)

