Resting-state fMRI:
Applications in Cognitive and Clinical Neuroscience

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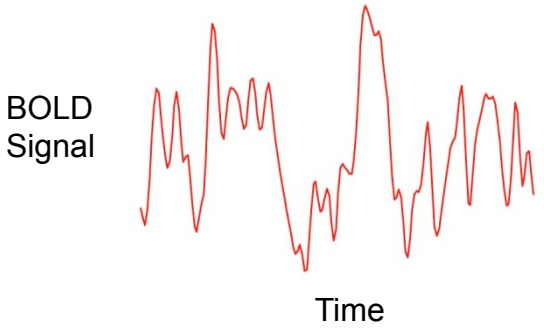
Overview

- Numerous intrinsic connectivity networks
- Relation to normal brain function
  - Functional correlates of network strength
  - Effect of fluctuations on evoked behavior/responses
  - Connectivity to study continuous, subject-driven states
- Relevance to neuropsychiatric diseases
  - Neurodegenerative diseases
  - Coma, epilepsy, depression

Functional Connectivity

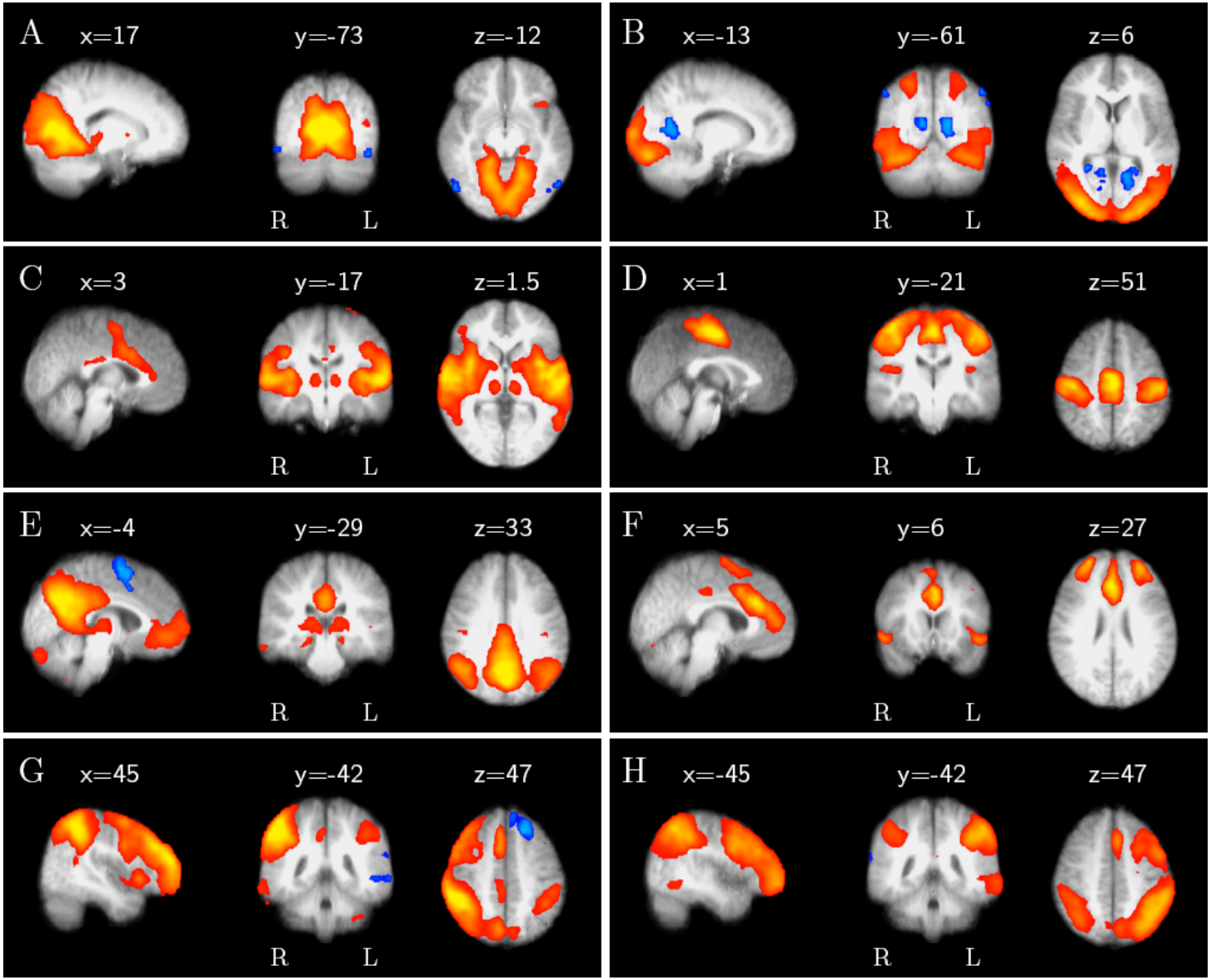


r = 0.80

r = 0.59

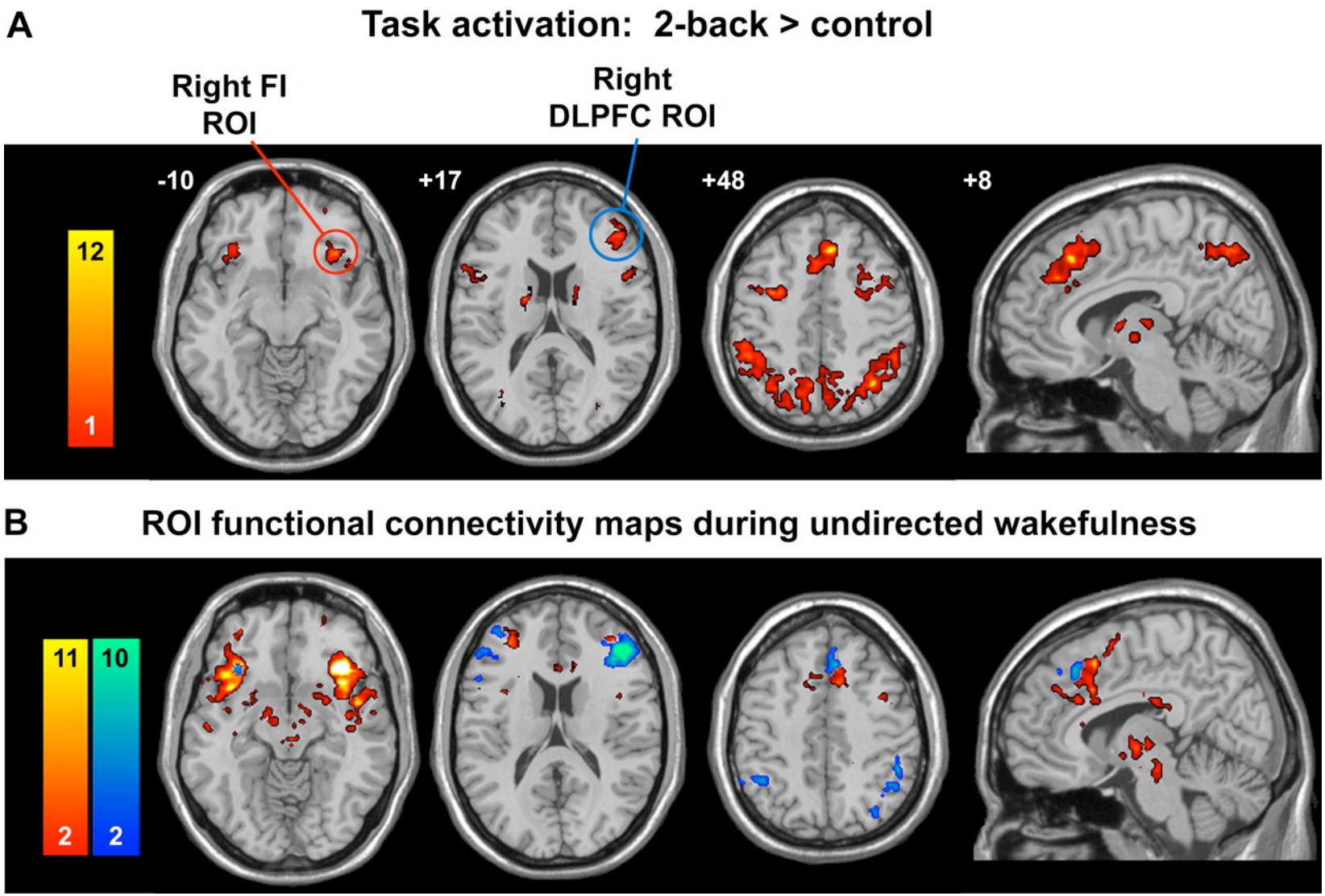
r = 0.75

A Network for Every Function and a Function for Every Network



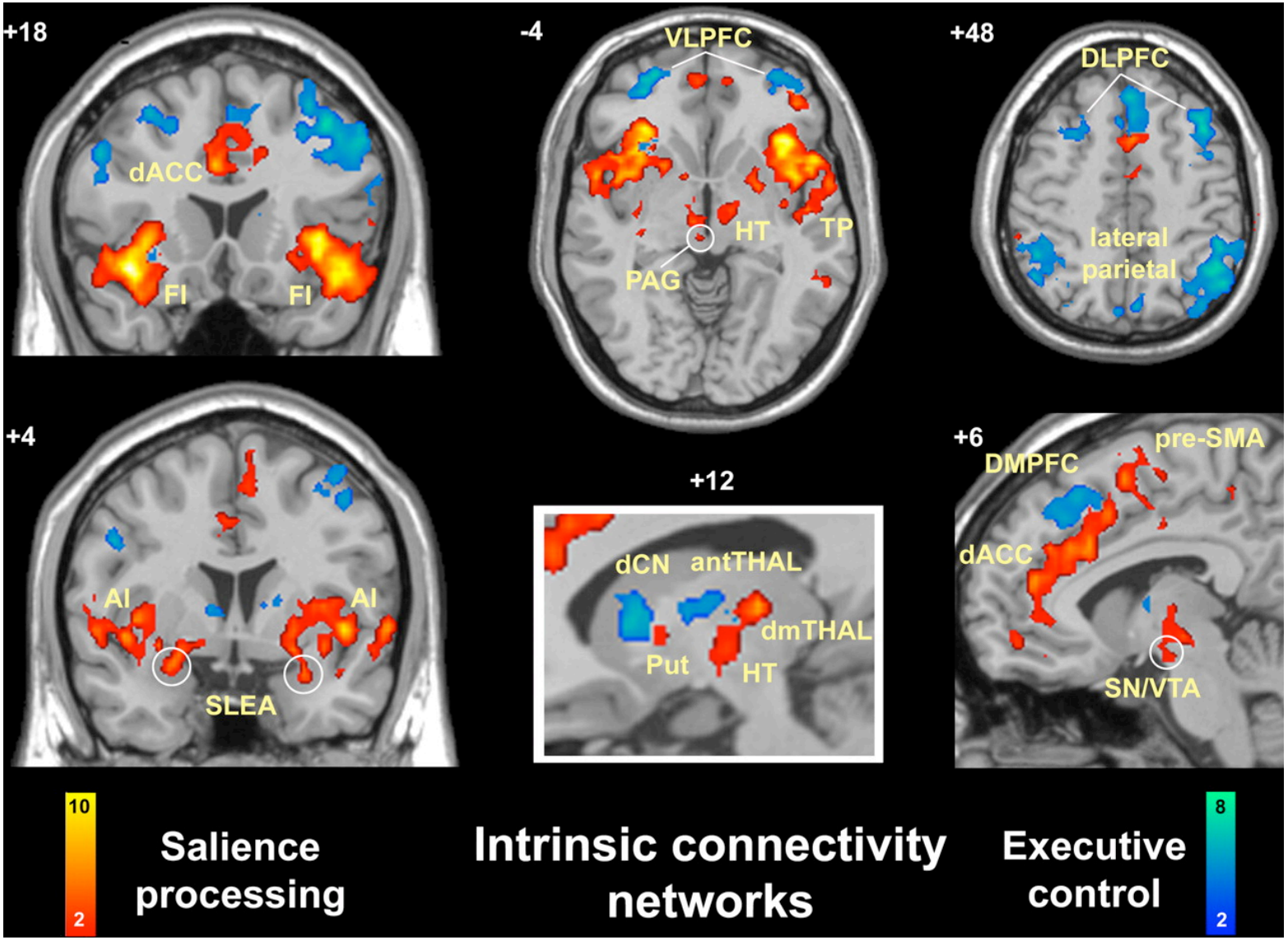
Beckmann et al., *Philos Trans R Soc Lond*, 2005

ICNs for Salience Detection and Executive Control



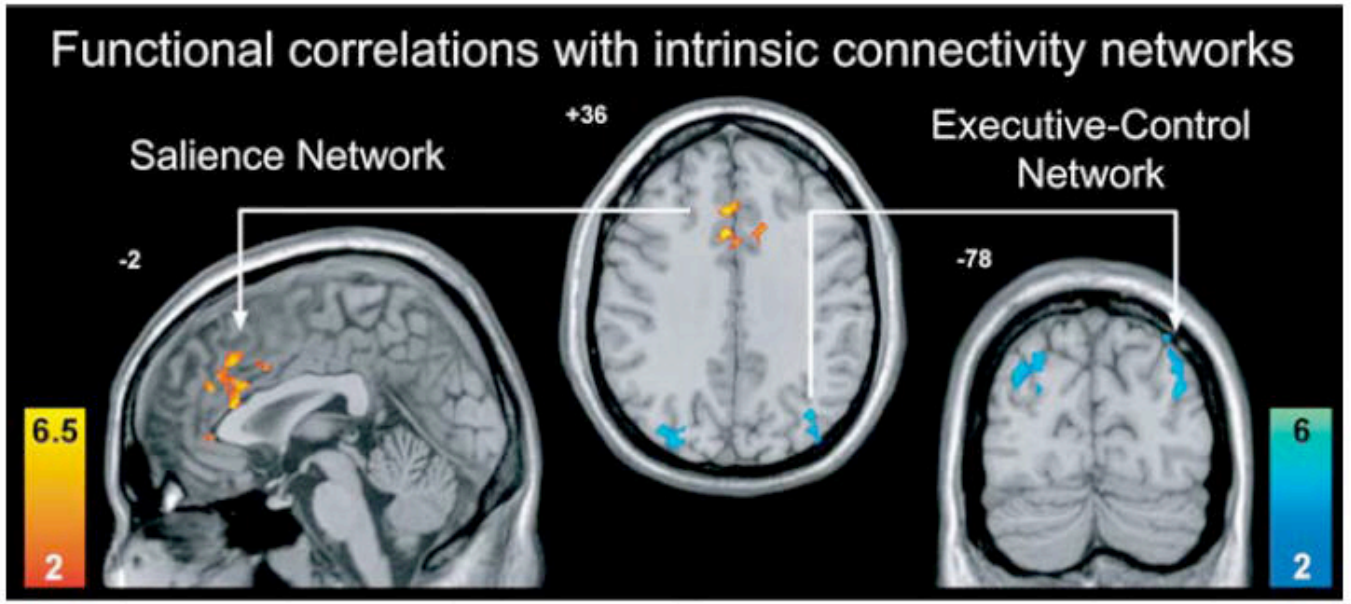
Seeley et al., *J Neurosci*, 2007

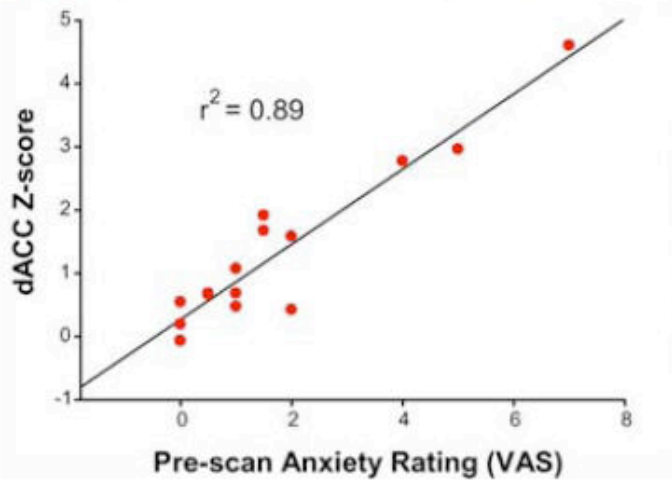
Replicated with Independent Component Analysis

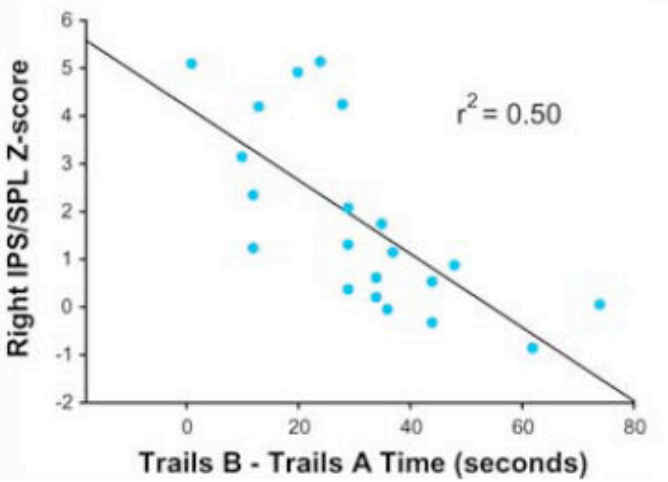


Seeley et al., *J Neurosci*, 2007

Correlations with Behavior

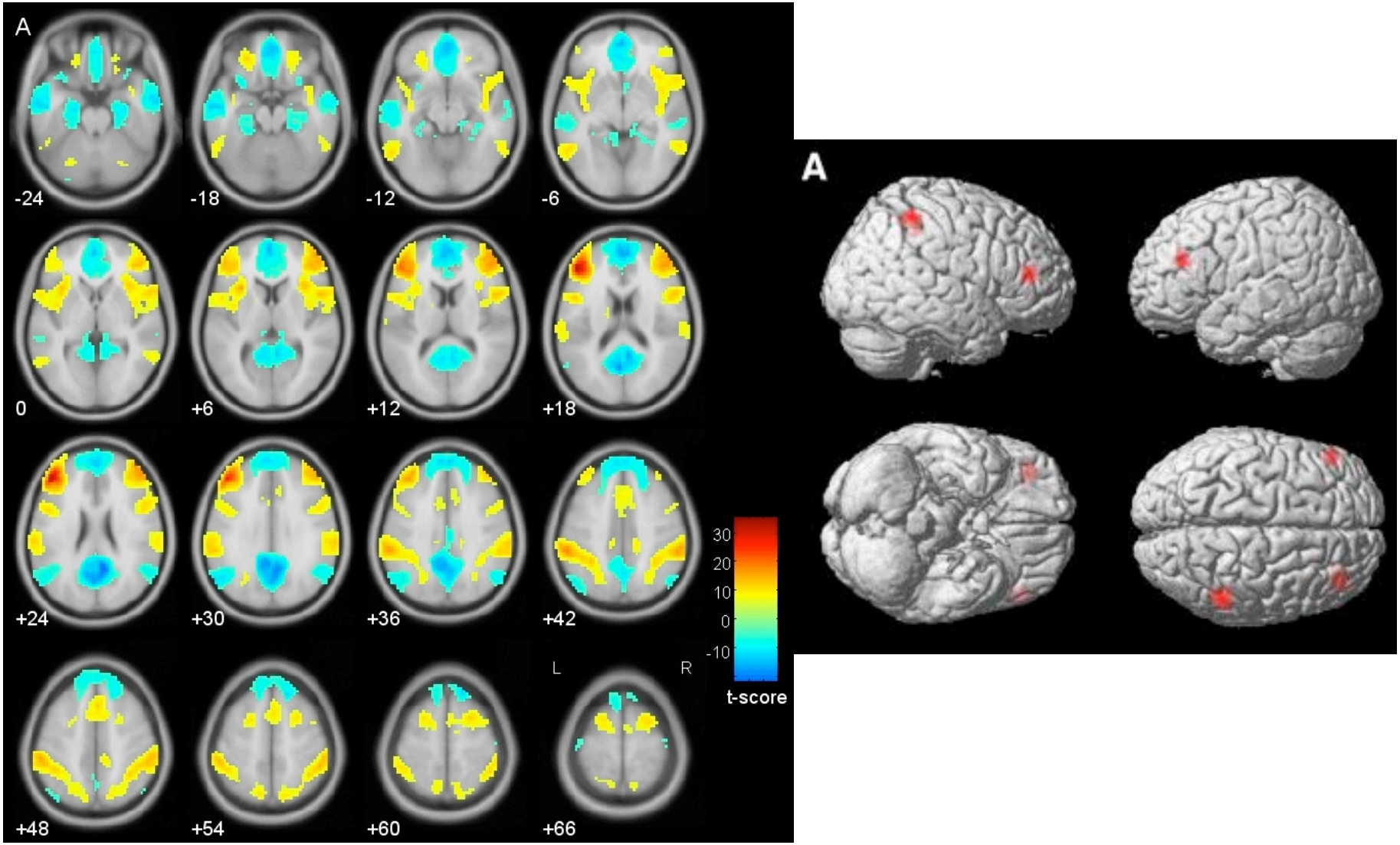






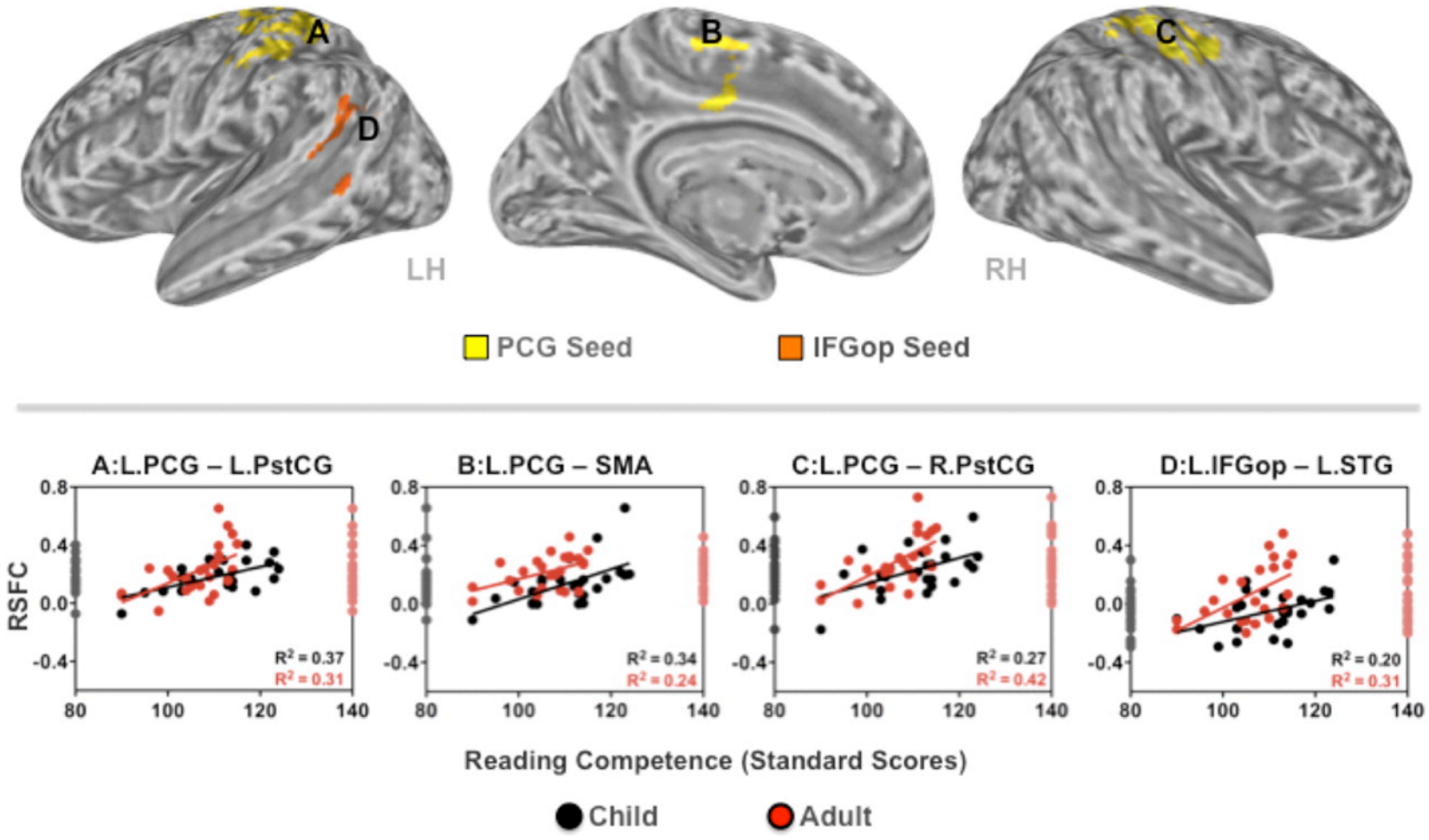
Seeley et al., *J Neurosci*, 2007

ECN Correlates with IQ



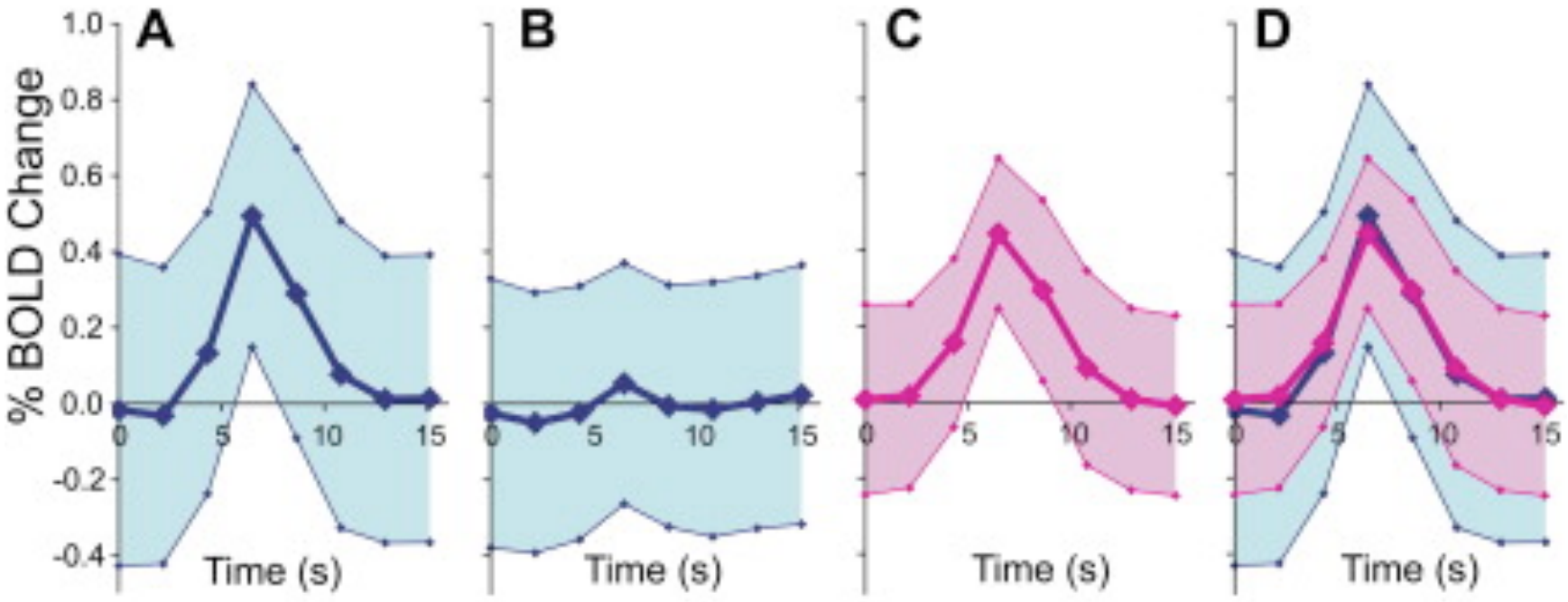
Song et al., *Neuroimage*, 2008

Left Inferior Frontal to Superior Temporal Connectivity Correlates with Reading Competence



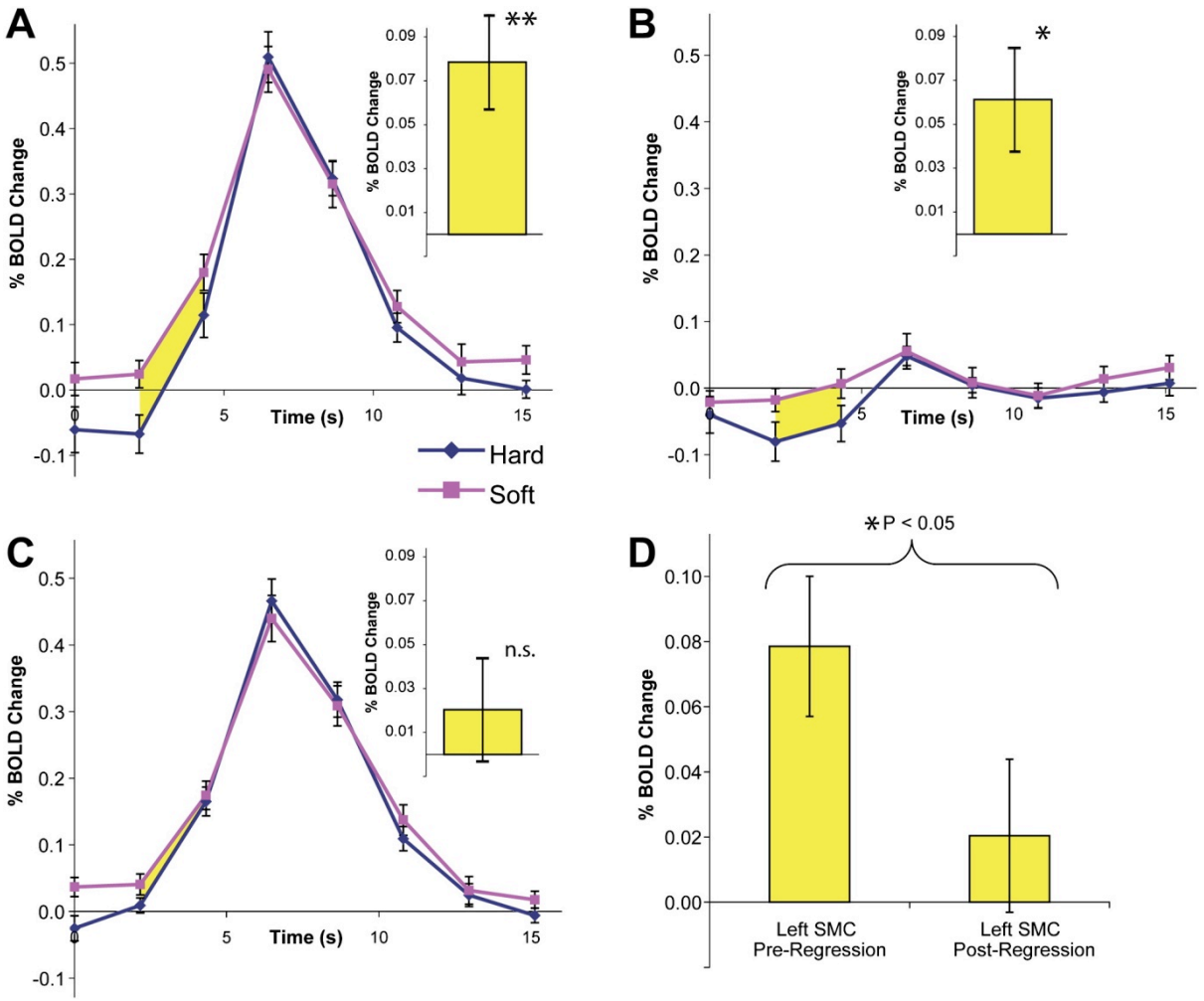
Koyama et al., *J Neurosci*, 2011

Spontaneous Fluctuations and Intertrial Variability



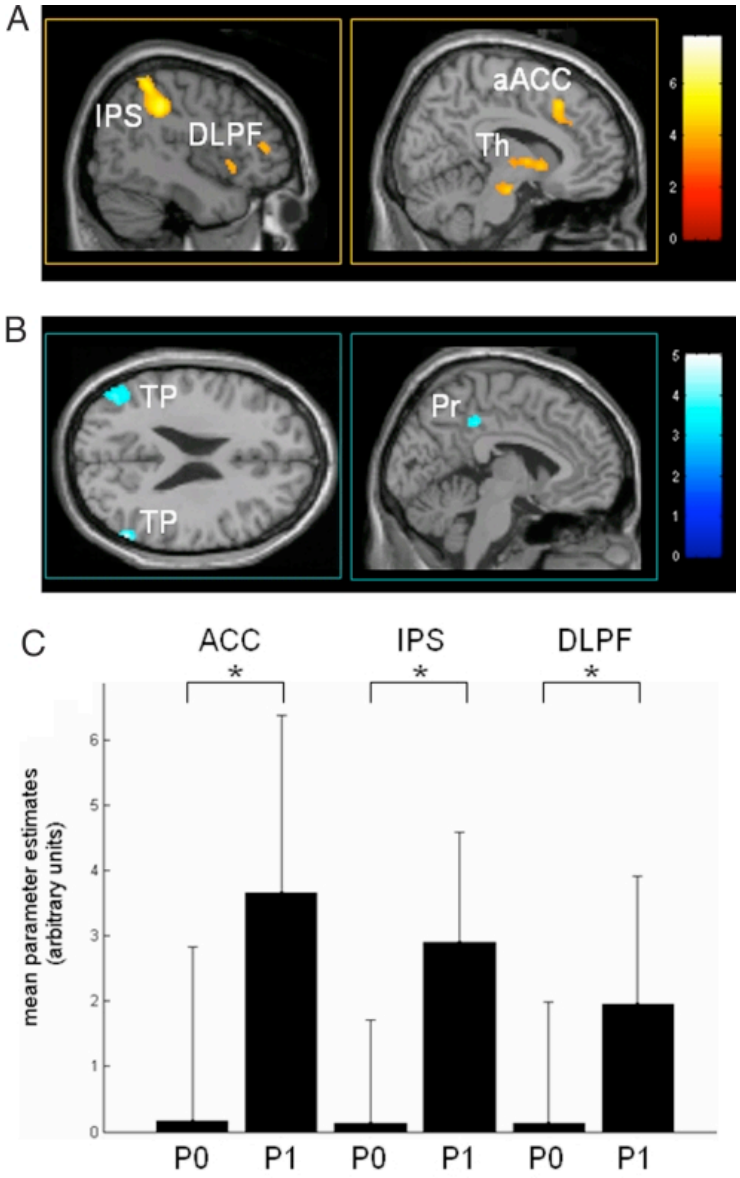
Fox et al., *Neuron*, 2007

Spontaneous Fluctuations and Behavior 1



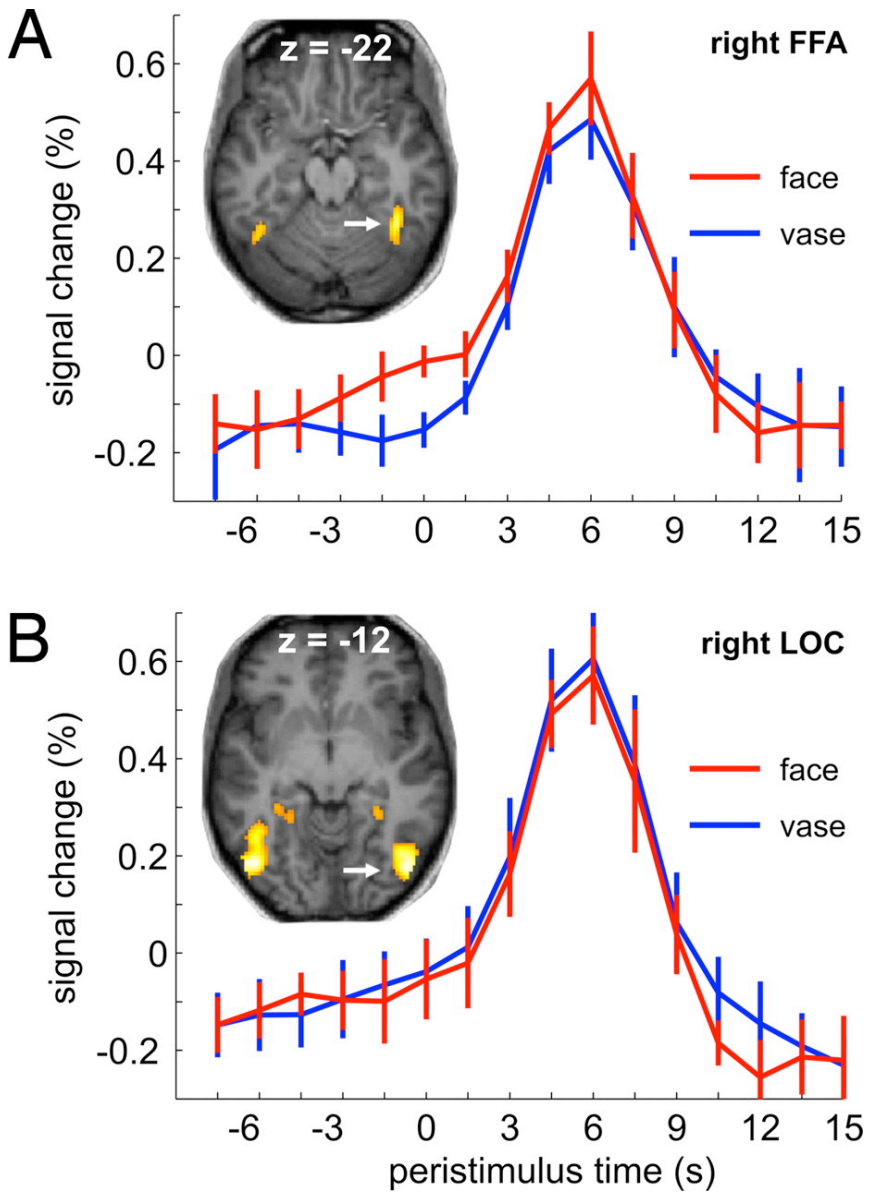
Fox et al., *Neuron*, 2007

Spontaneous Fluctuations and Behavior 2



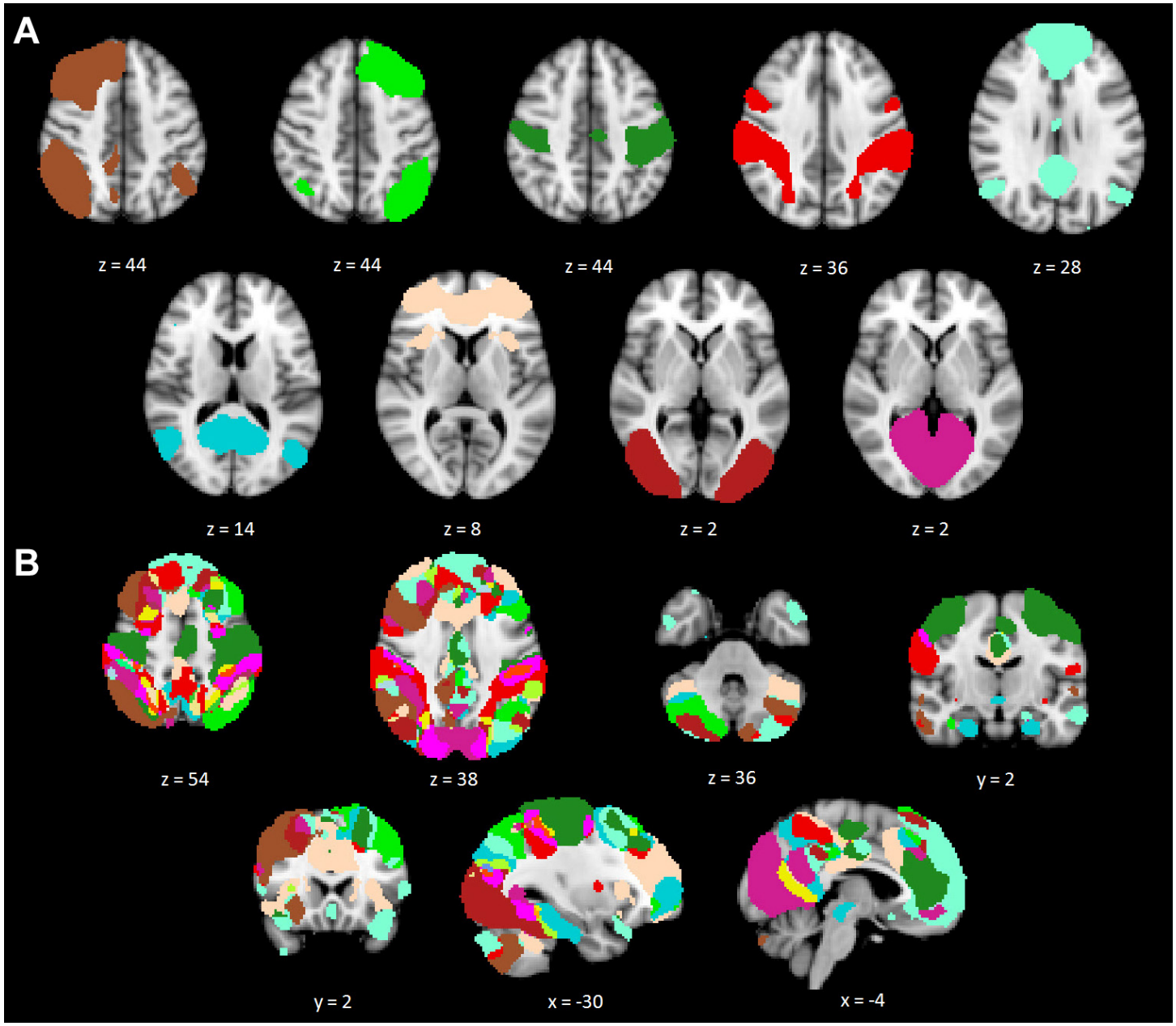
Boly et al.,
PNAS 2007

Spontaneous Fluctuations and Behavior 3

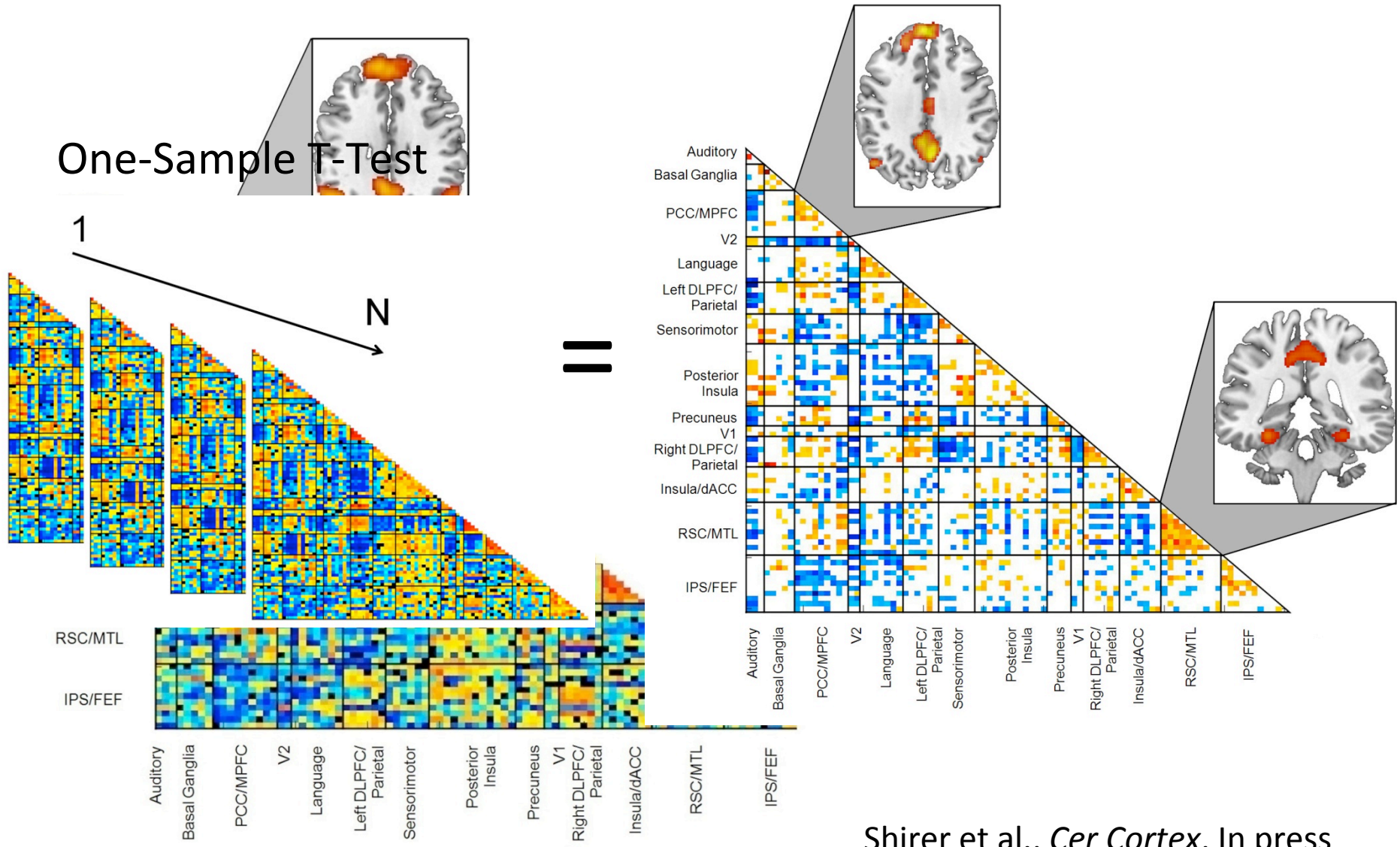


Hesselmann et al.,
PNAS 2008

Whole-Brain Connectivity

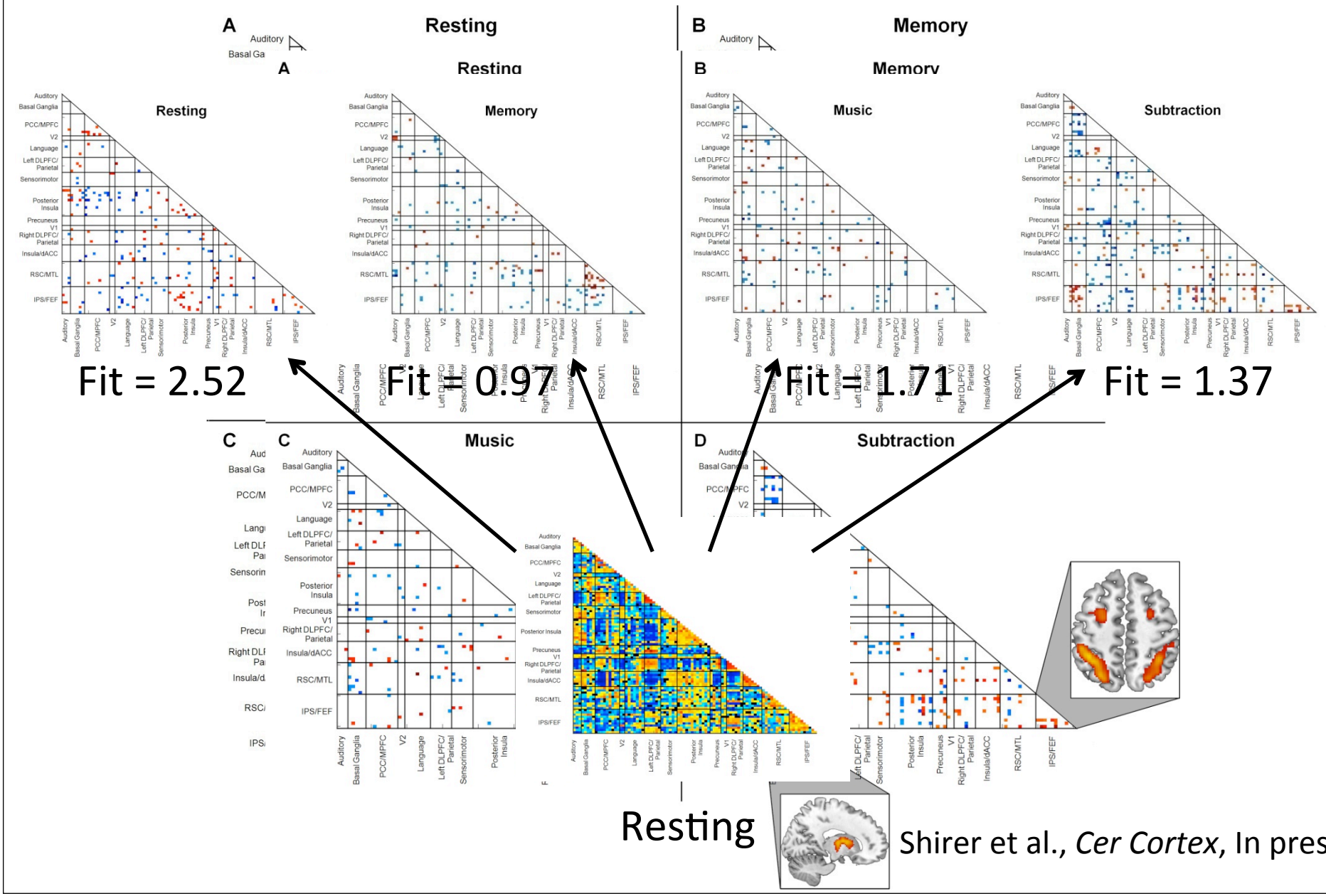


Defining Continuous, Subject-Driven



Shirer et al., *Cer Cortex*, In press

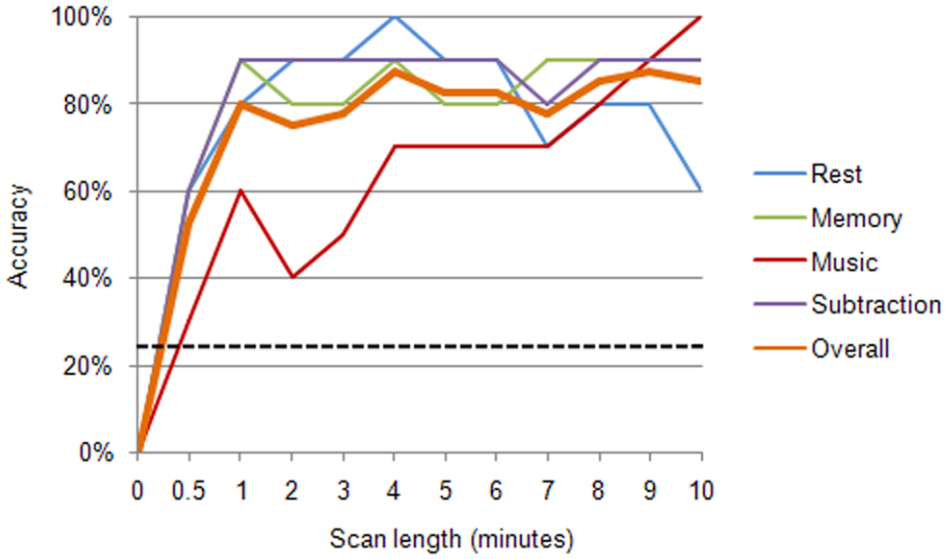
Classification



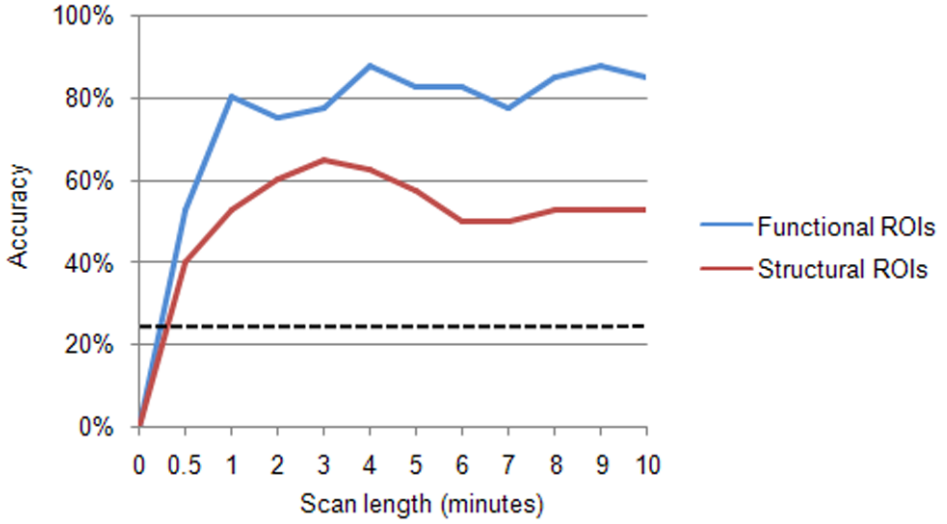
Shirer et al., *Cer Cortex*, In press

Accuracy

LOOCV: 84% (47 of 56)
Independent Sample: 85% (34 of 40)

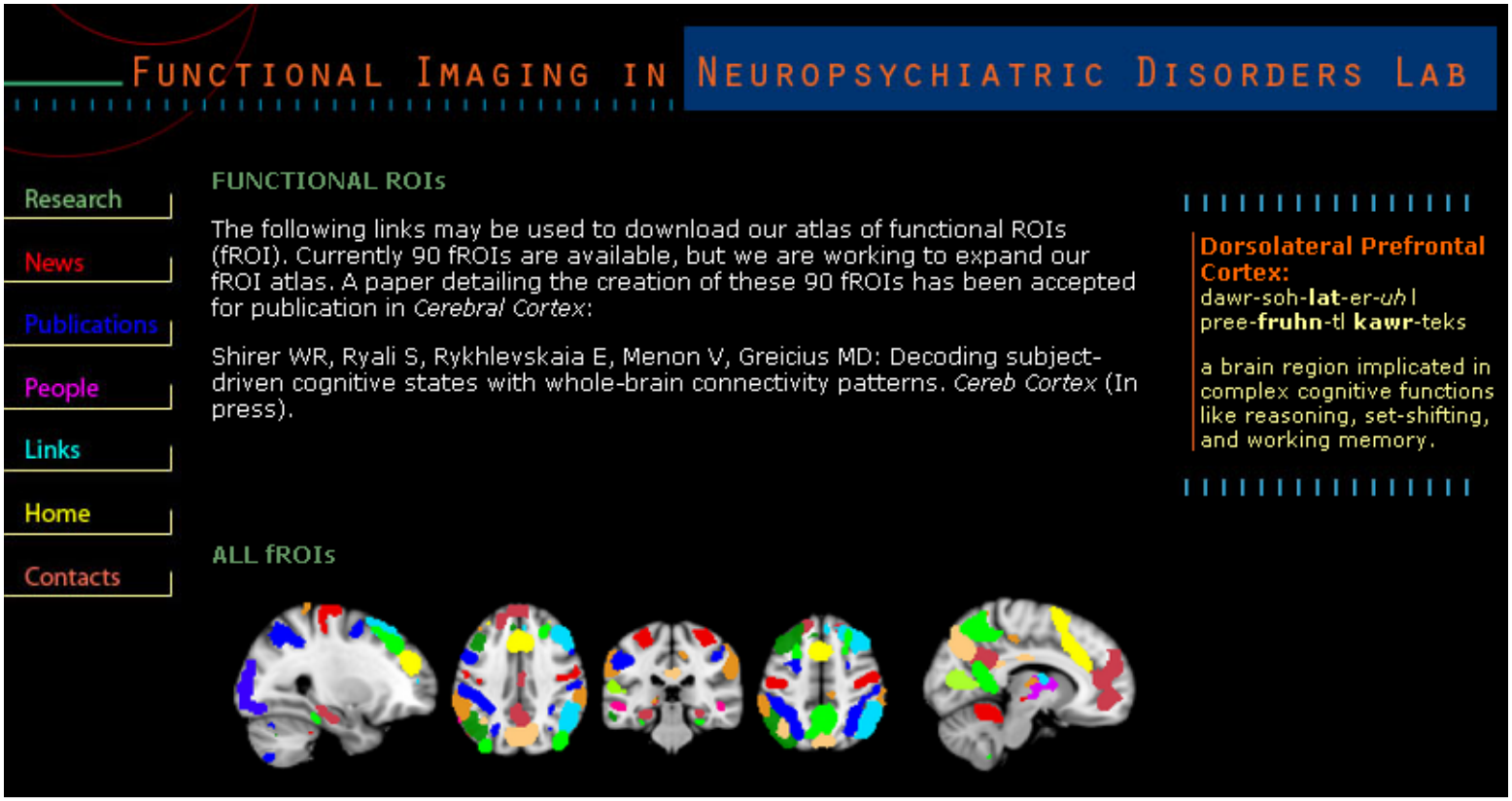


Structural ROIs (AAL): 65% (26 of 40)
fROIs > AAL for all scan lengths ($p < 0.001$)

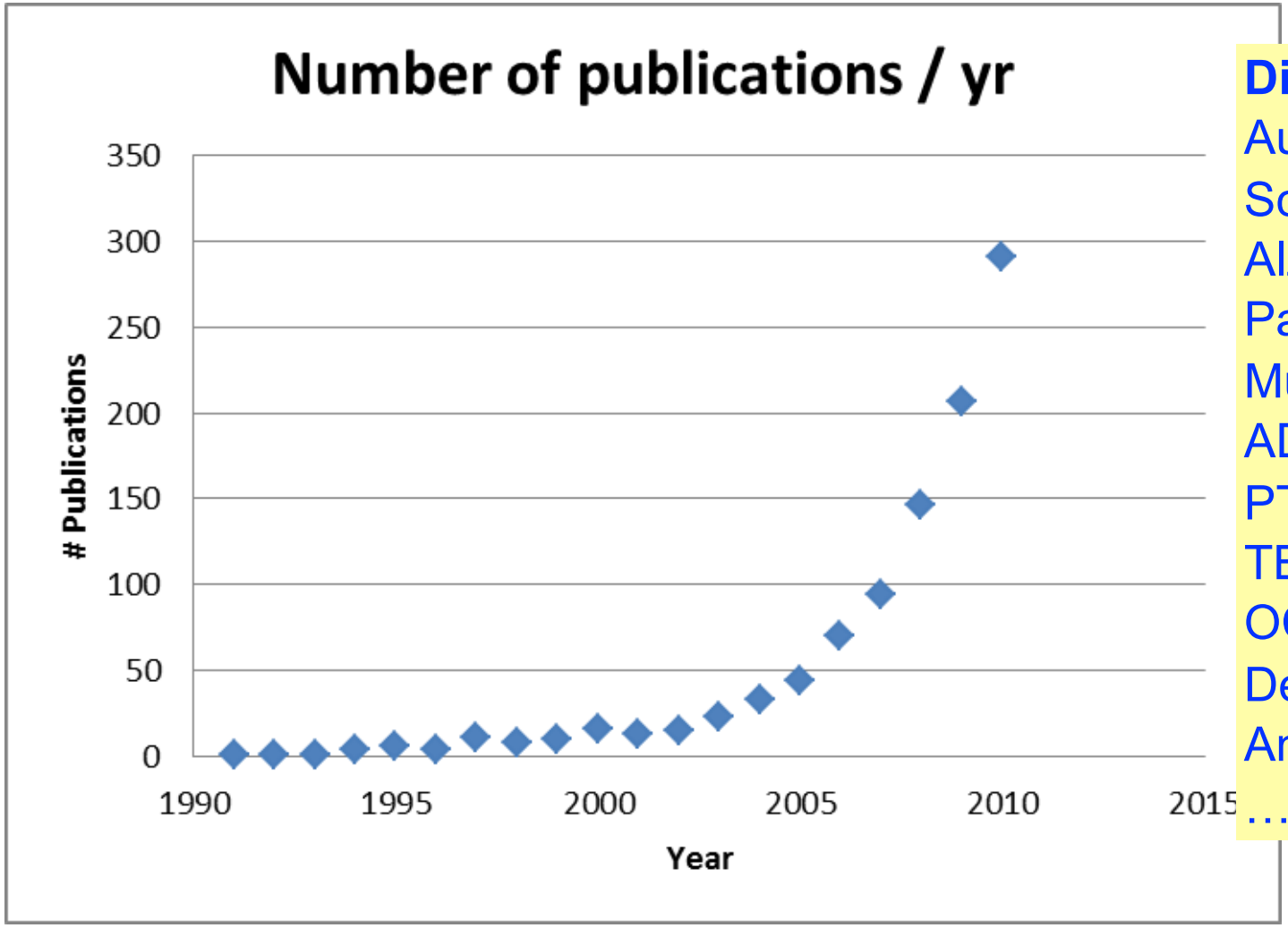


Shirer et al., *Cer Cortex*, In press

Functional ROIs Available:



Exponential Growth of Resting State fMRI Studies

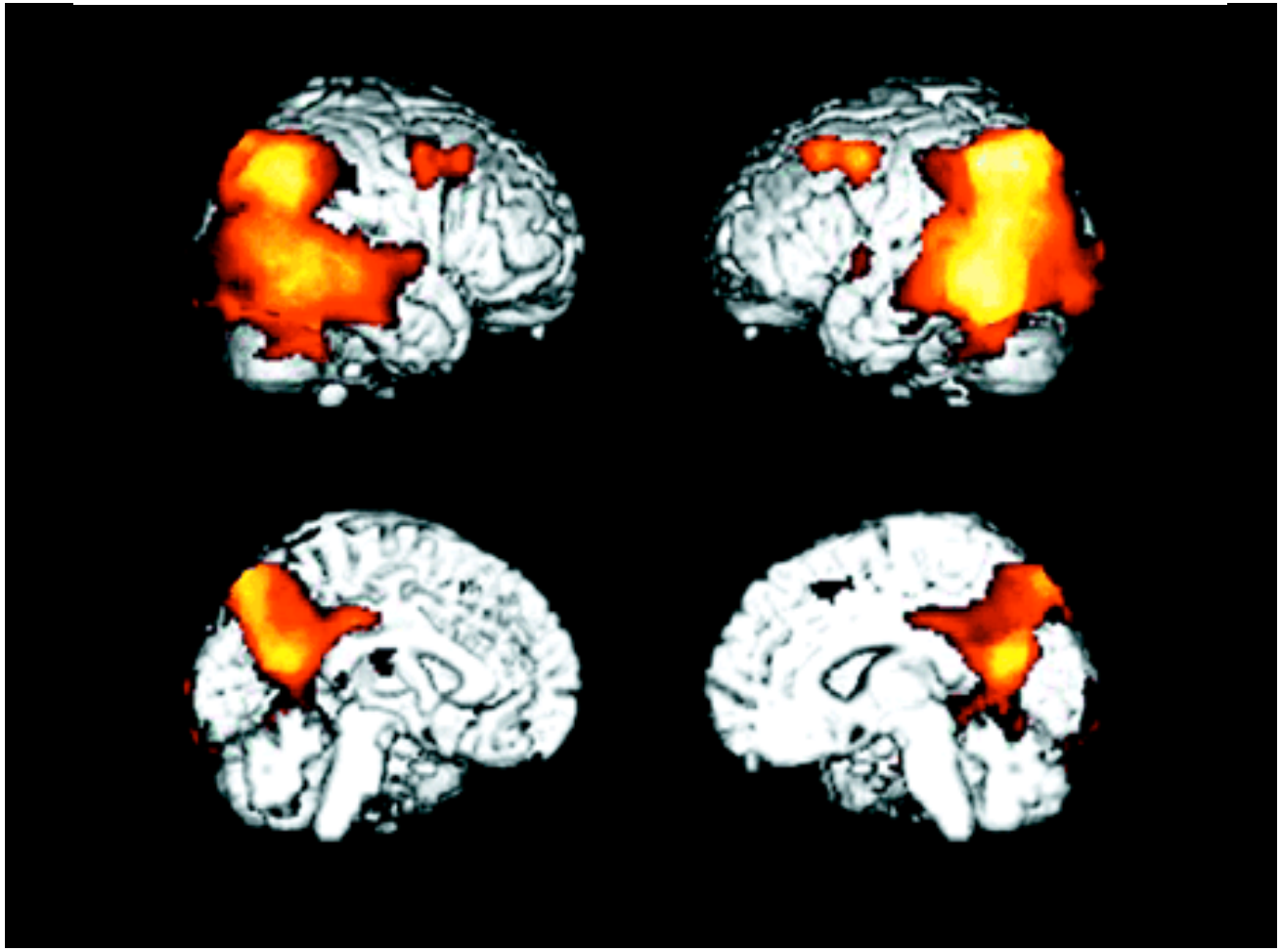


Disorders Studied

Autism
Schizophrenia
Alzheimer's Disease
Parkinson's Disease
Multiple Sclerosis
ADHD
PTSD
TBI
OCD
Depression/Bipolar
Anxiety Disorder
…

Slide and scopus search courtesy of Rasmus Birn,
Medical College of Wisconsin

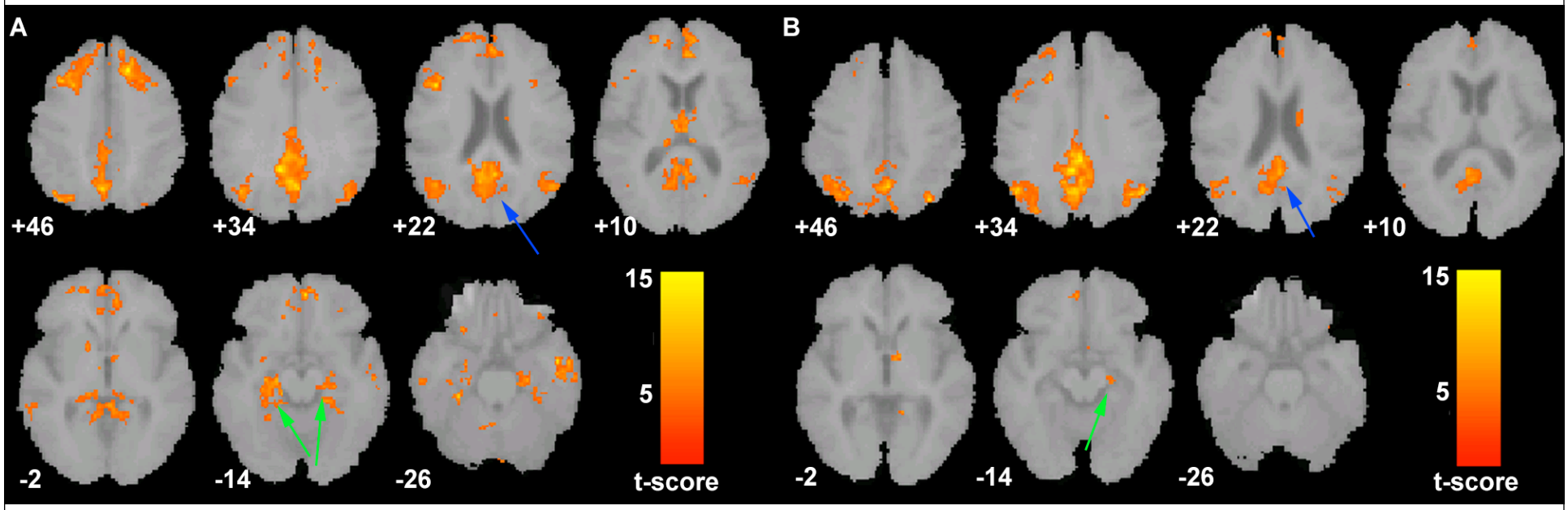
Hypometabolism in AD



Resting PET: 34 healthy subjects versus 14 AD patients.

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

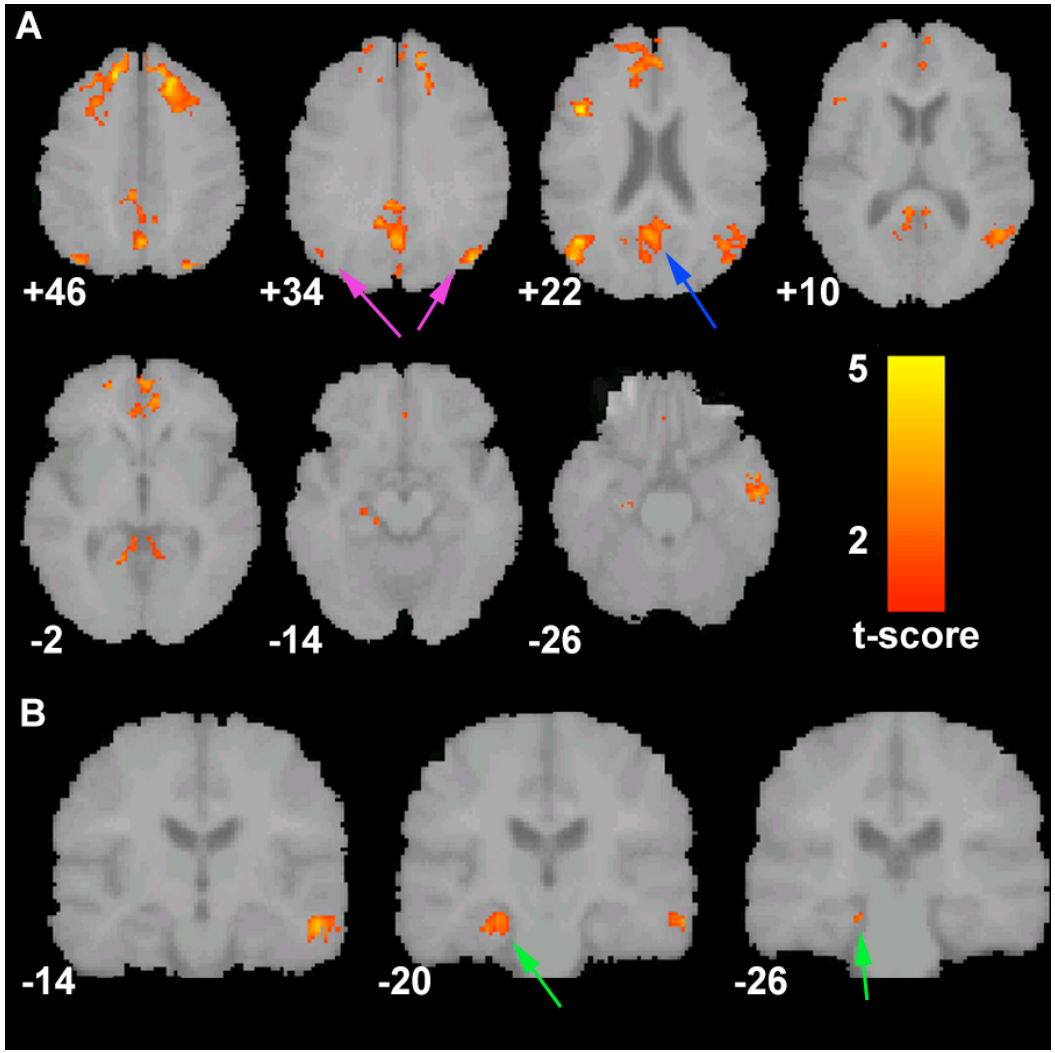
Default-Mode Network in AD



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

Greicius et al., *PNAS*, 2004

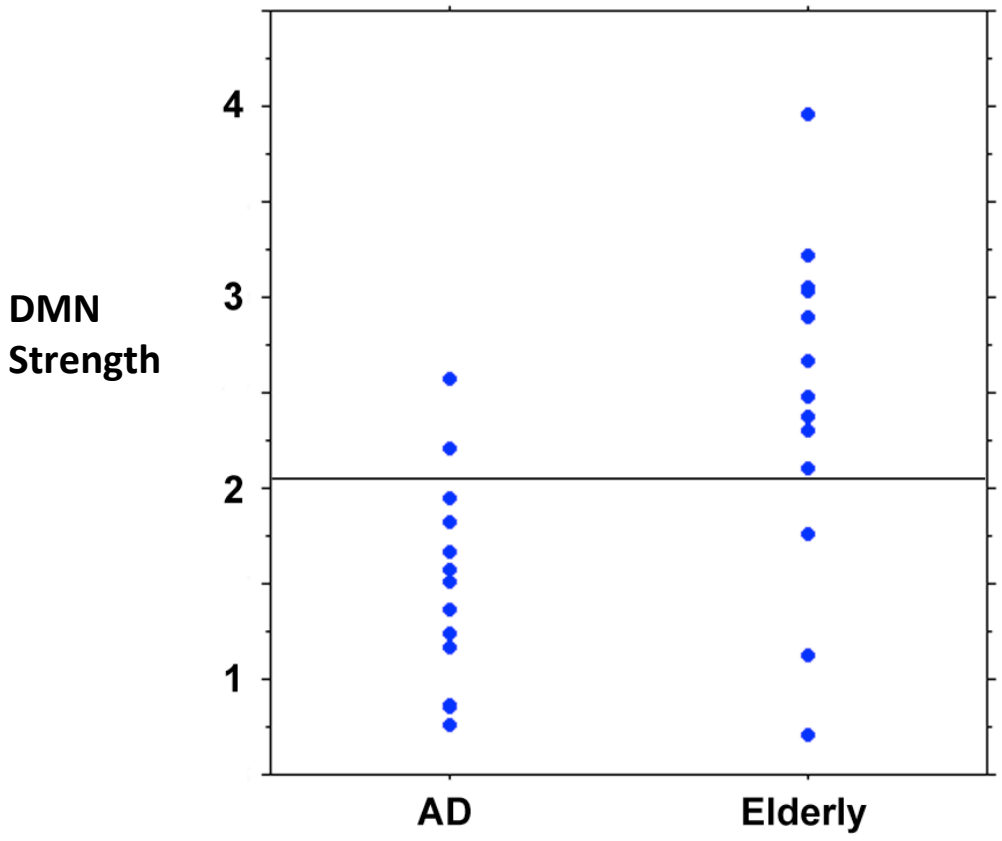
Default-mode in healthy aging versus



Greicius et al., *PNAS*, 2004

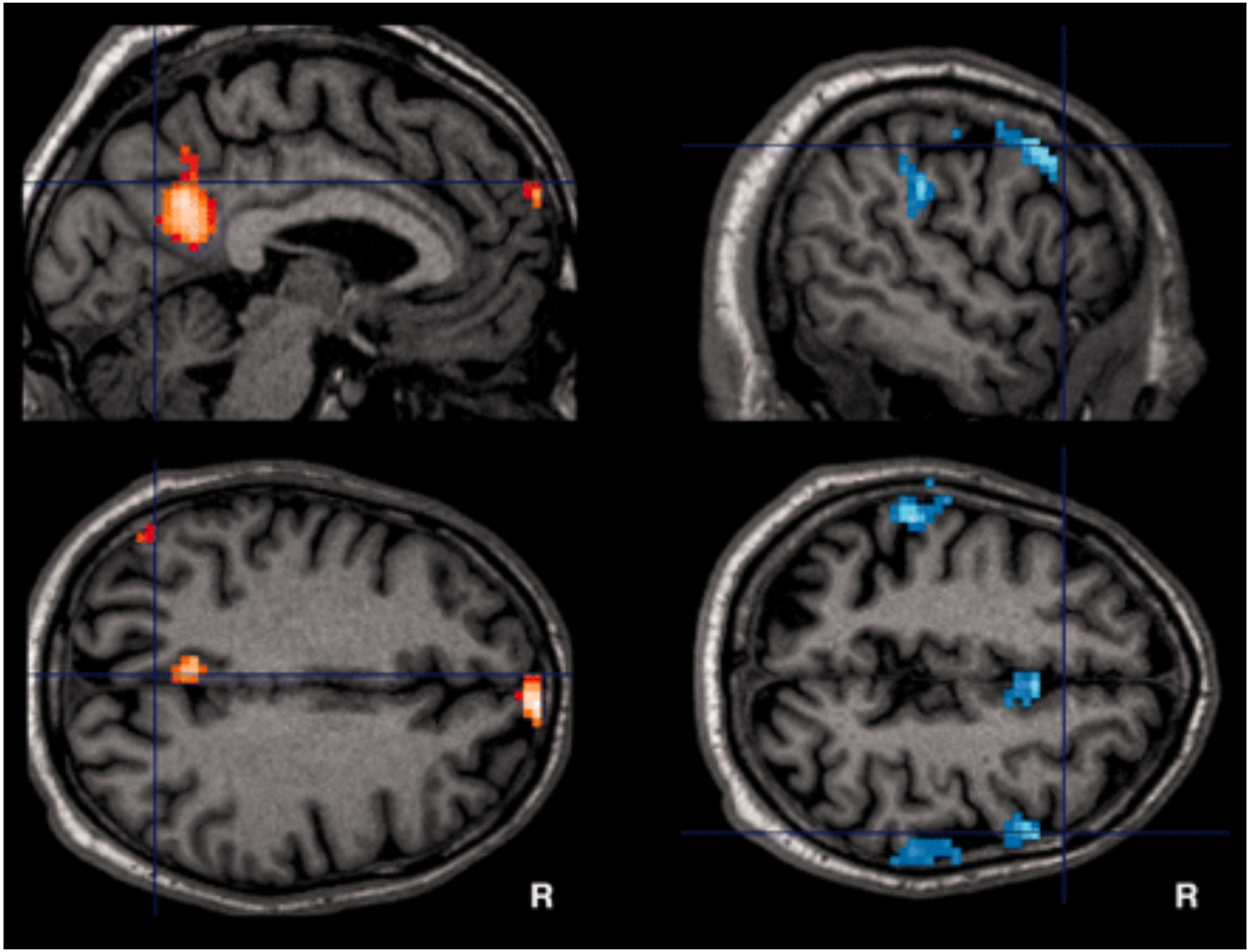
Single-Subject DMN Measure

85% sensitivity
77% specificity



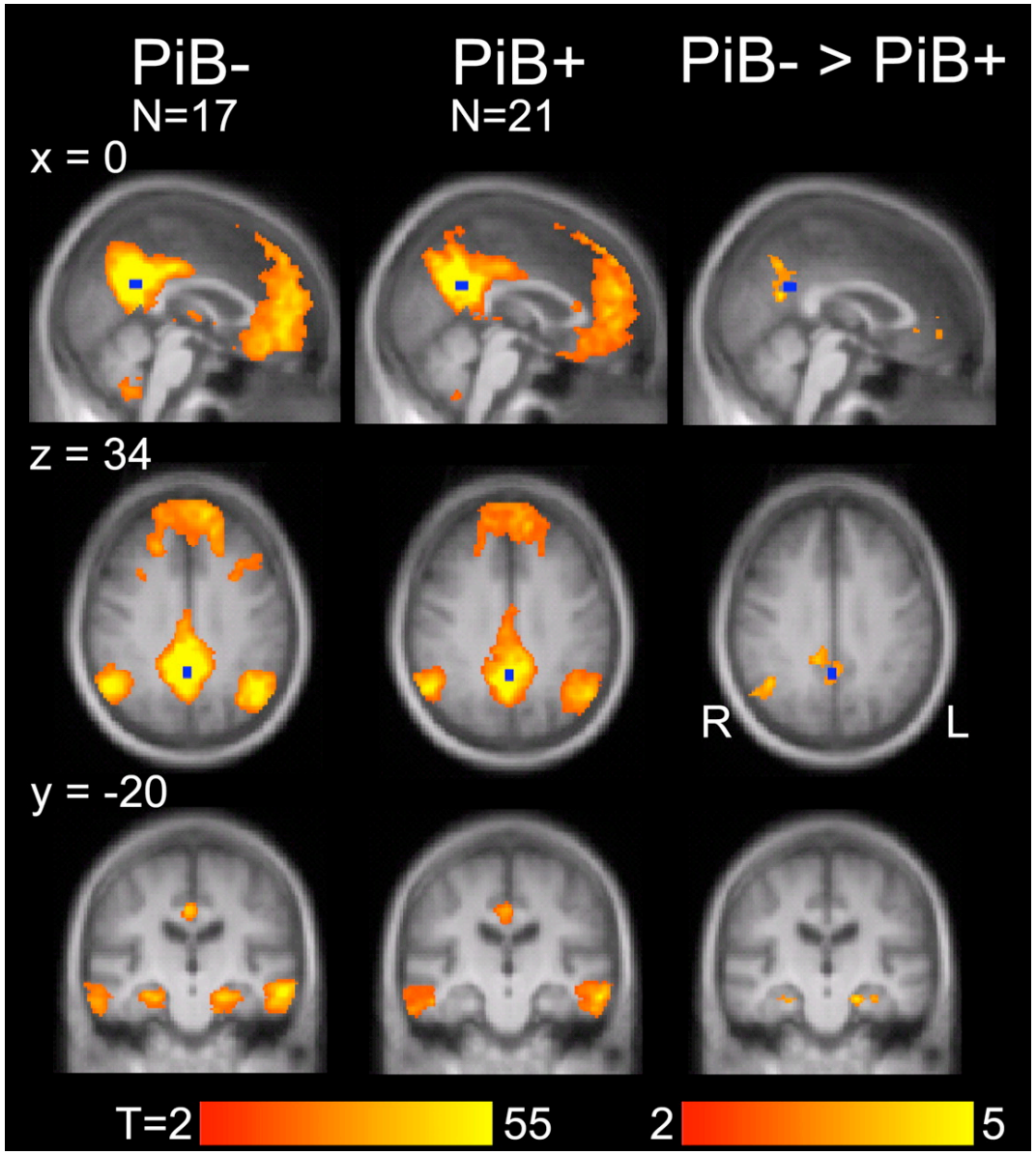
Greicius et al., *PNAS*, 2004

Reduced DMN Connectivity in MCI



Sorg et al., *PNAS* 2007

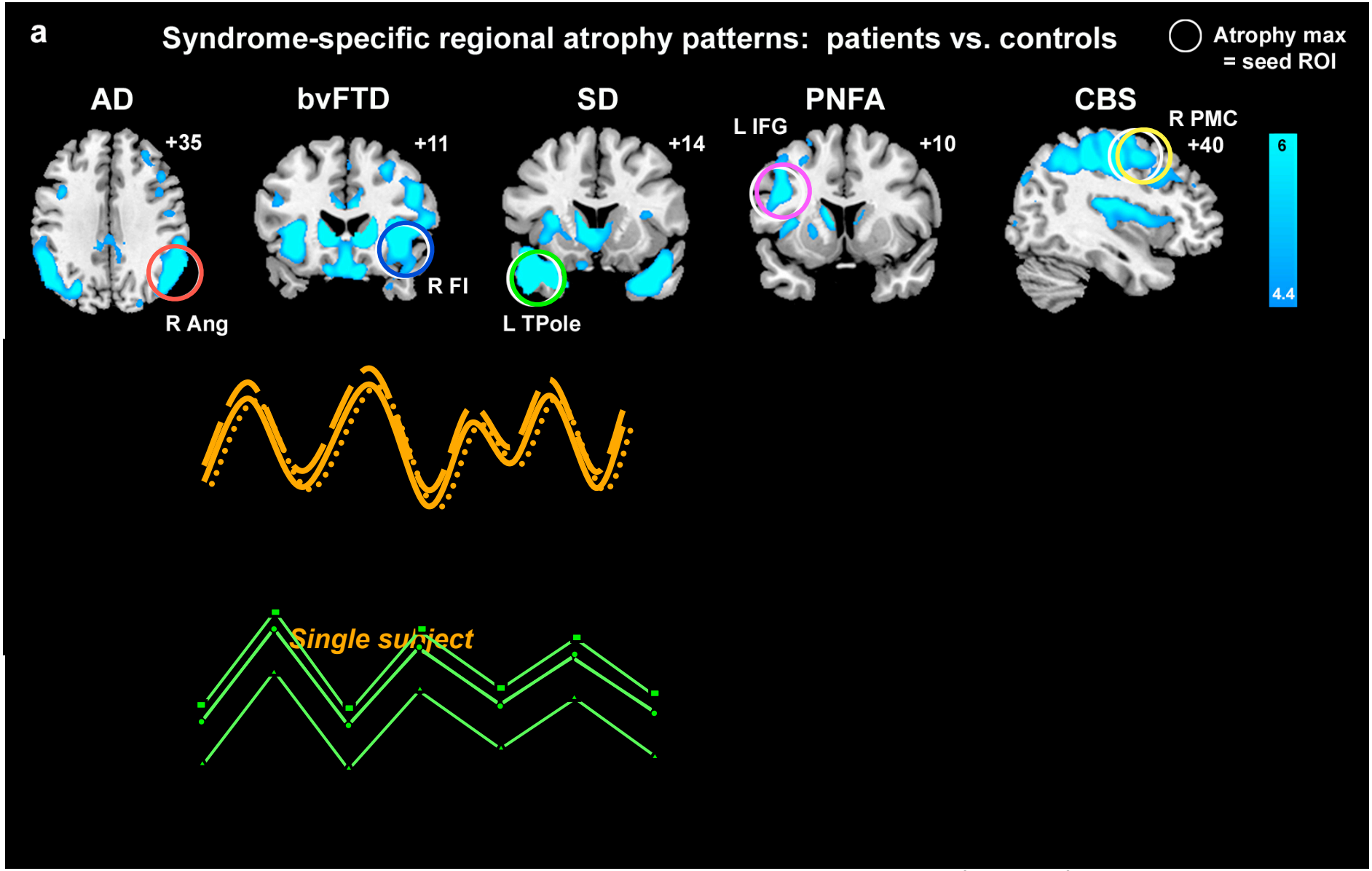
Reduced DMN Connectivity in PIB+ Controls



Hedden et al., *J Neurosci,* 2009
Sheline et al., *Biol Psych* 2010

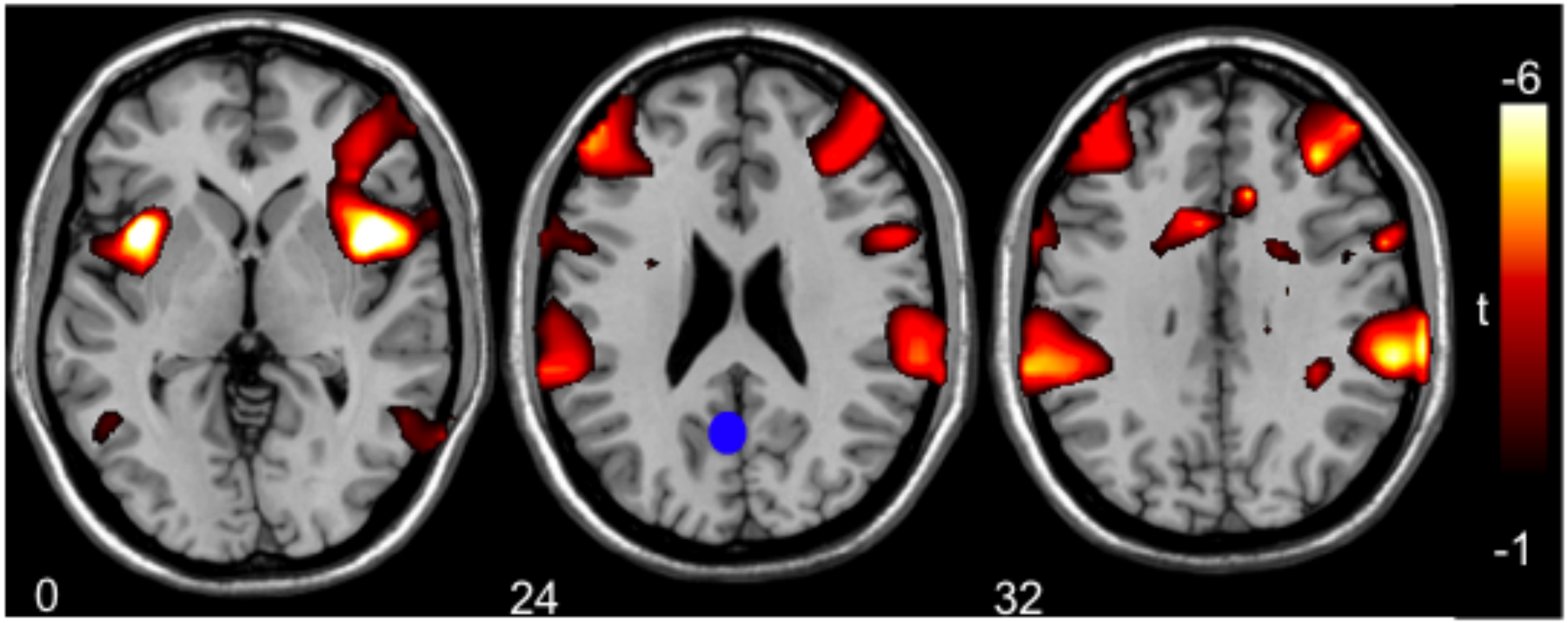
Network-Based Neurodegeneration

Fire Together, Wire Together, Expire Together



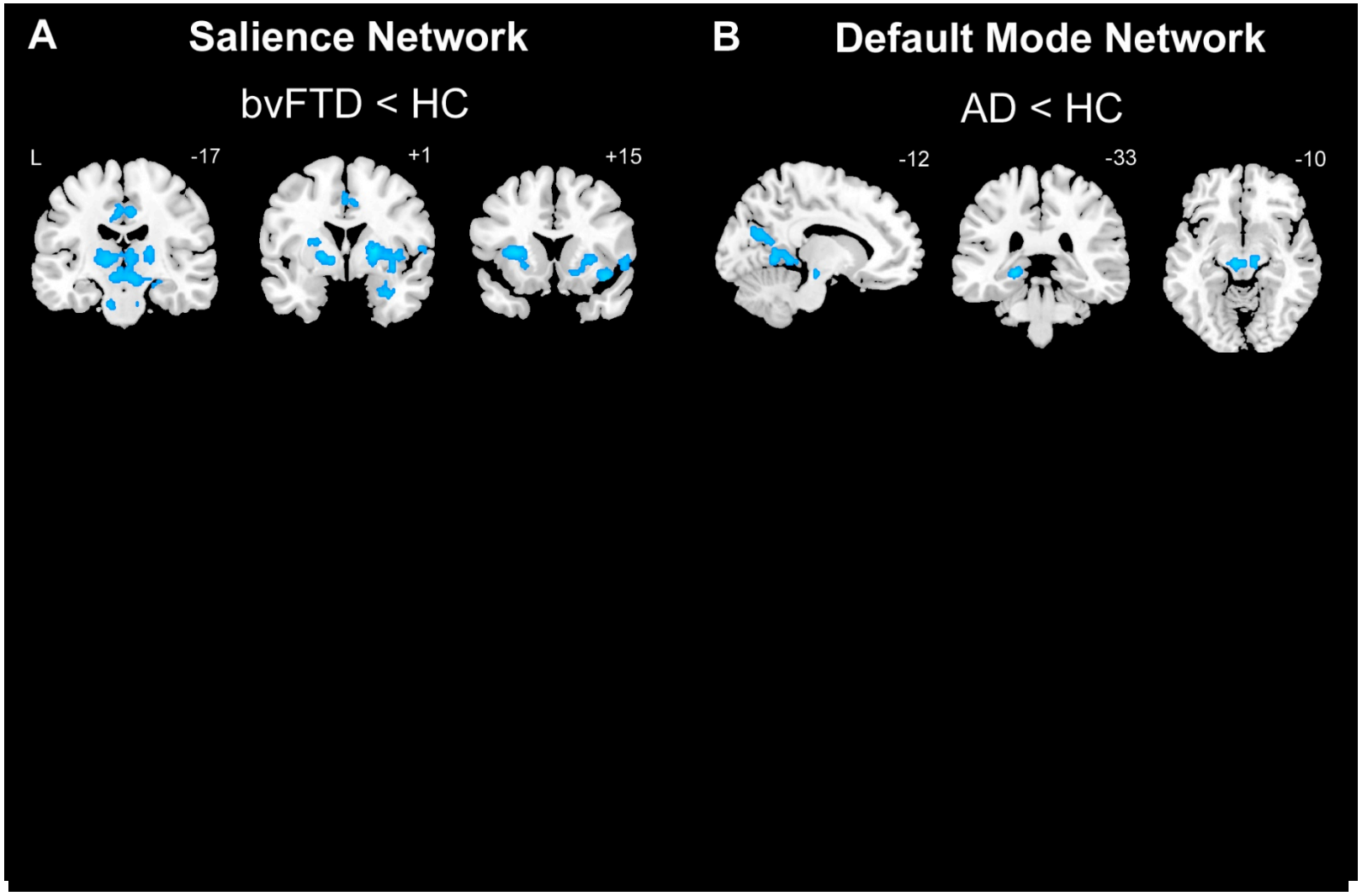
Seeley et al., *Neuron*, 2009

Anti-Correlations without Global Scaling (Group Level)



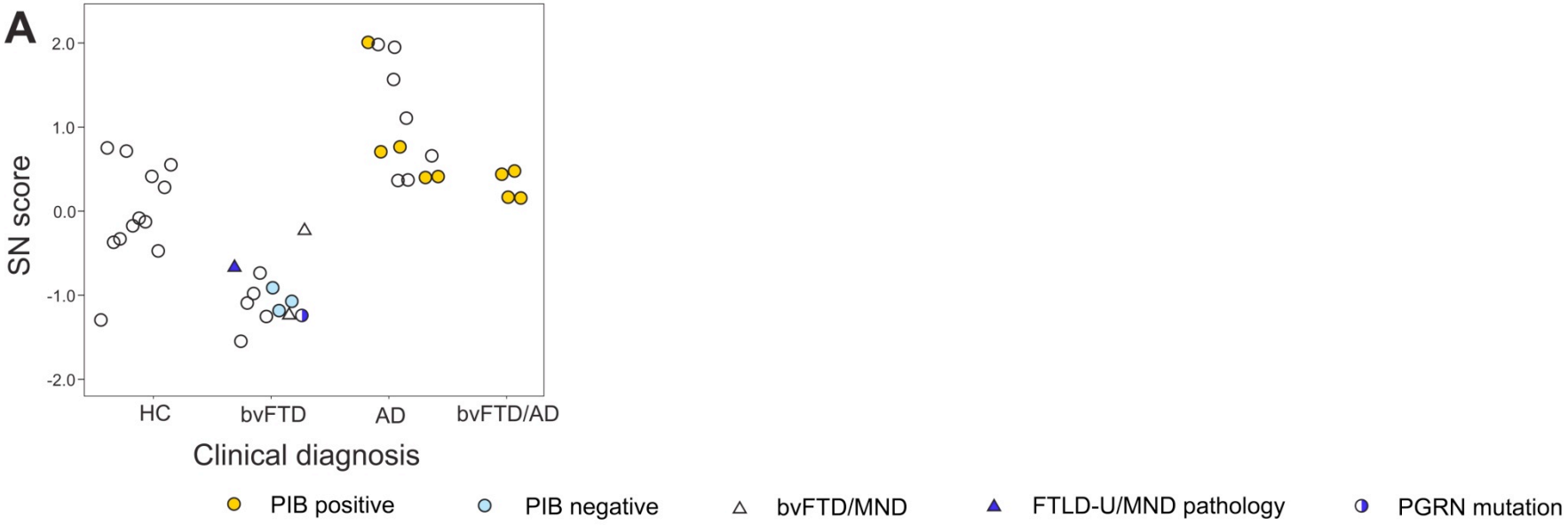
Chang and Glover, Neuroimage 2010

FTD vs AD = Salience vs DMN



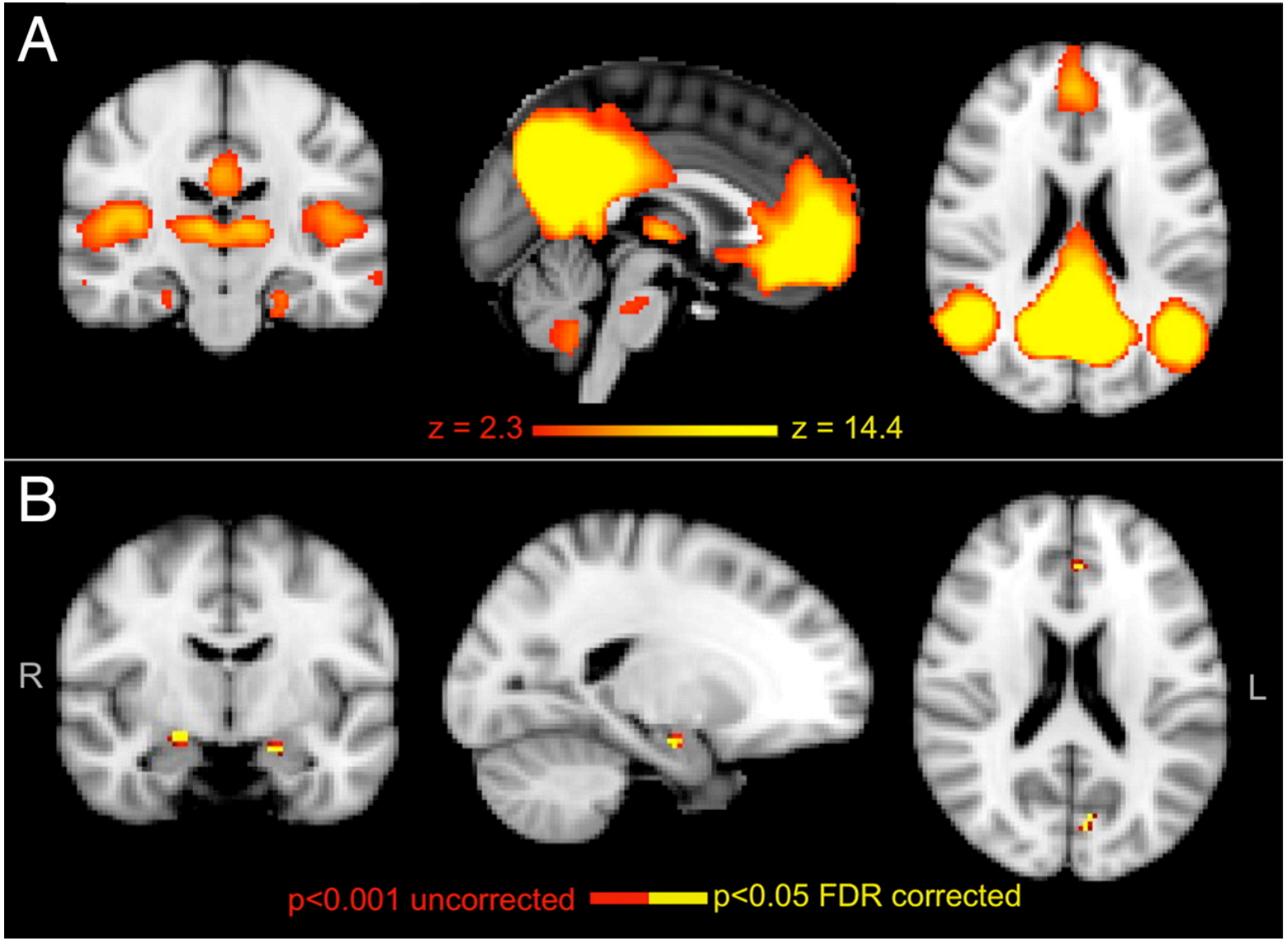
Zhou et al., *Brain* , 2010

FTD vs AD = Salience vs DMN



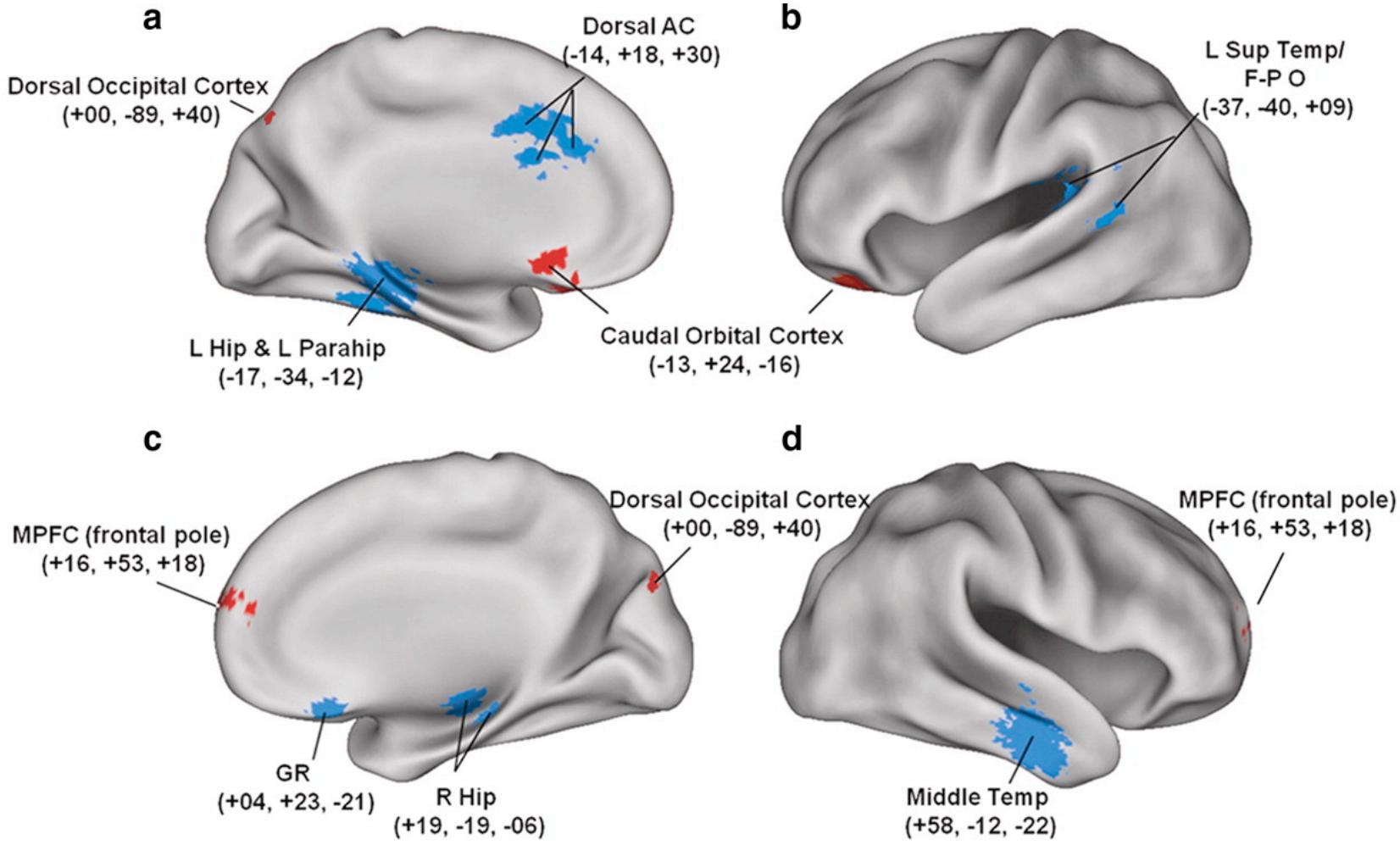
Zhou et al., *Brain* , 2010

Increased Connectivity in Young ApoE4 Carriers



Filippini et al., *PNAS*, 2009

ApoE and Connectivity in Healthy Aging



38 E4s (29 female), 62 nonE4s
All PIB-
mean age 62

Sheline et al., *J Neurosci*, 2010

ApoE and Connectivity in Healthy Aging 2

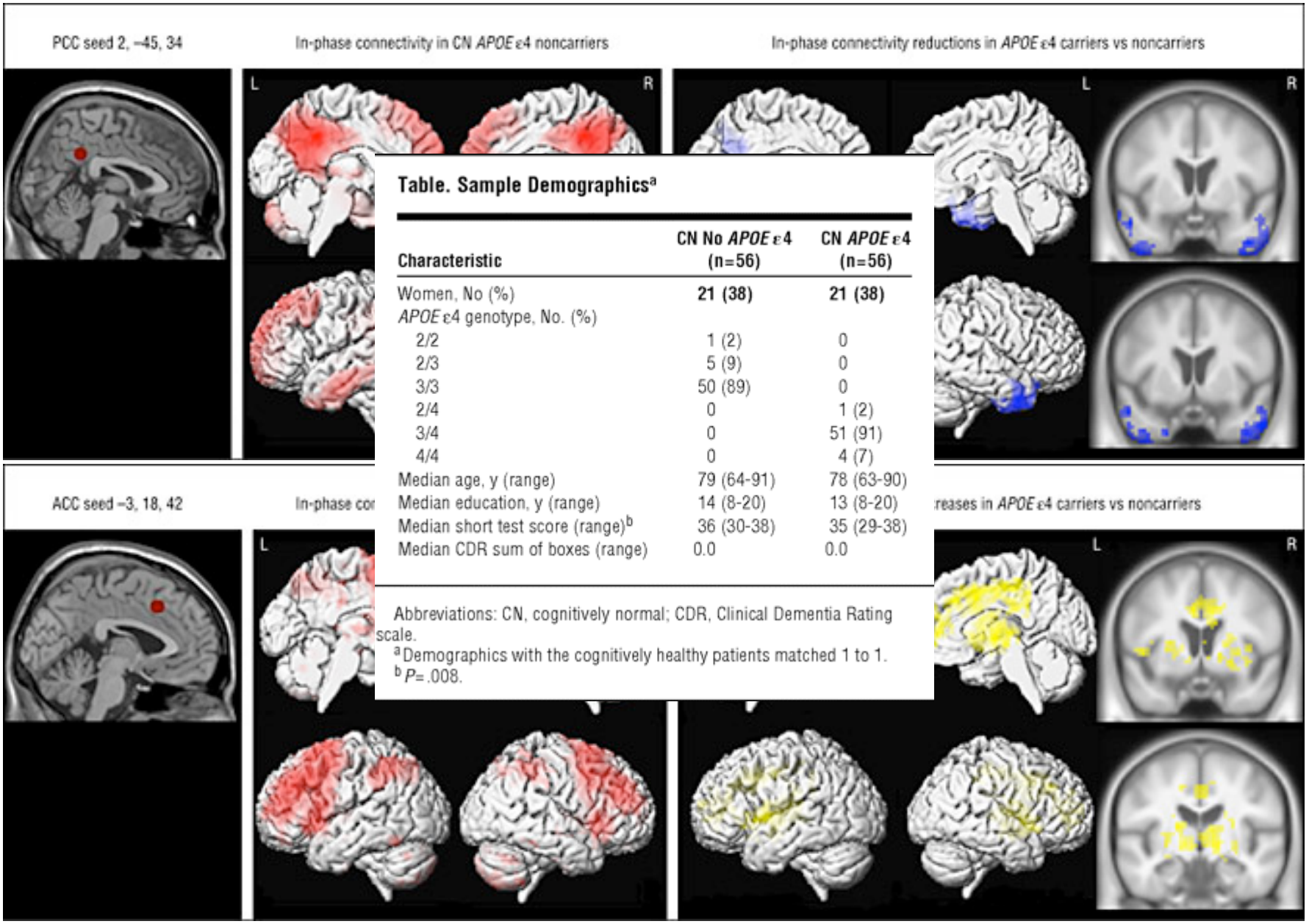


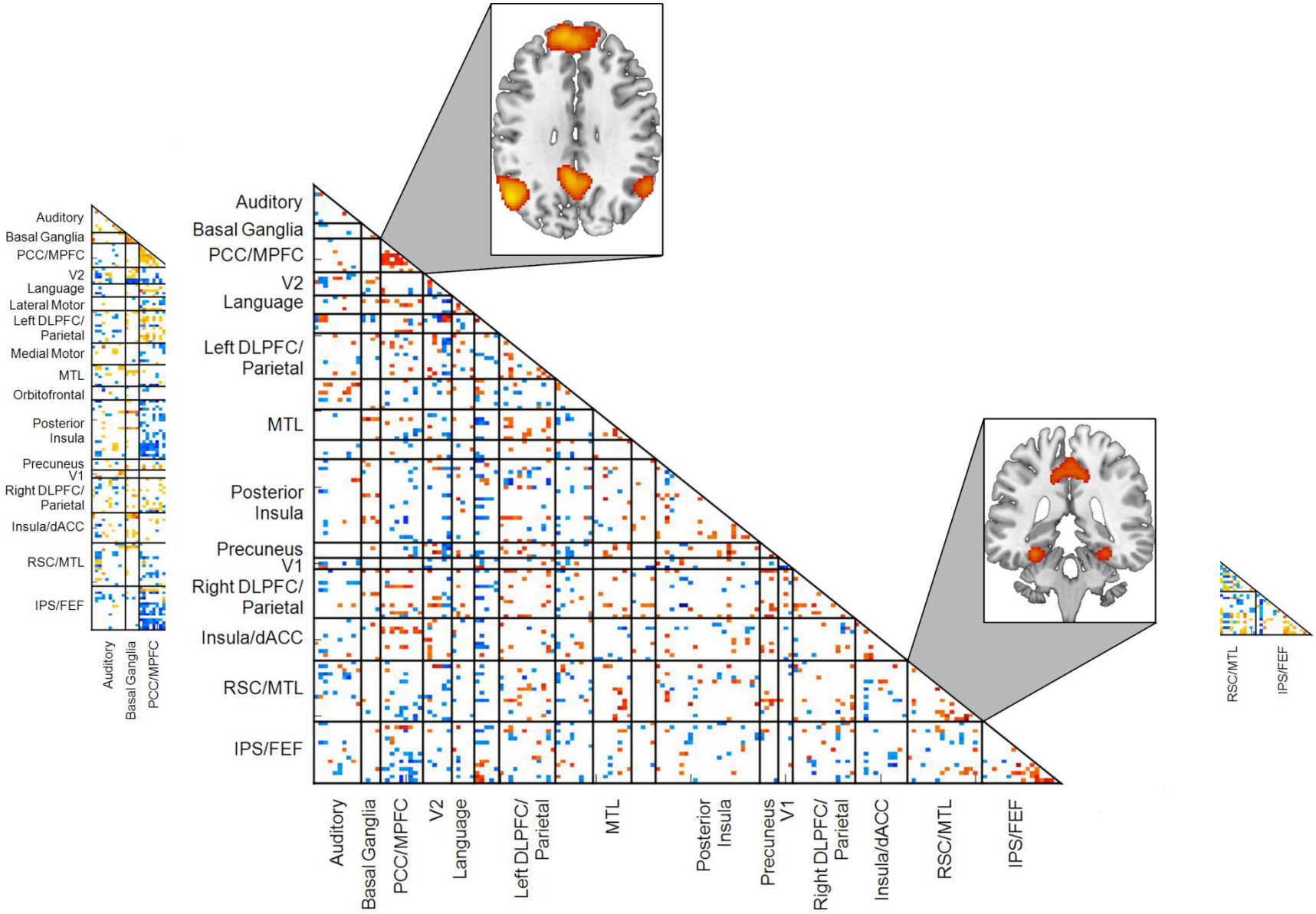
Table. Sample Demographics[a]

Characteristic	CN No *APOE* ε4 (n=56)	CN *APOE* ε4 (n=56)
Women, No (%)	**21 (38)**	**21 (38)**
APOE ε4 genotype, No. (%)		
2/2	1 (2)	0
2/3	5 (9)	0
3/3	50 (89)	0
2/4	0	1 (2)
3/4	0	51 (91)
4/4	0	4 (7)
Median age, y (range)	79 (64-91)	78 (63-90)
Median education, y (range)	14 (8-20)	13 (8-20)
Median short test score (range)[b]	36 (30-38)	35 (29-38)
Median CDR sum of boxes (range)	0.0	0.0

Abbreviations: CN, cognitively normal; CDR, Clinical Dementia Rating scale.
[a] Demographics with the cognitively healthy patients matched 1 to 1.
[b] $P = .008$.

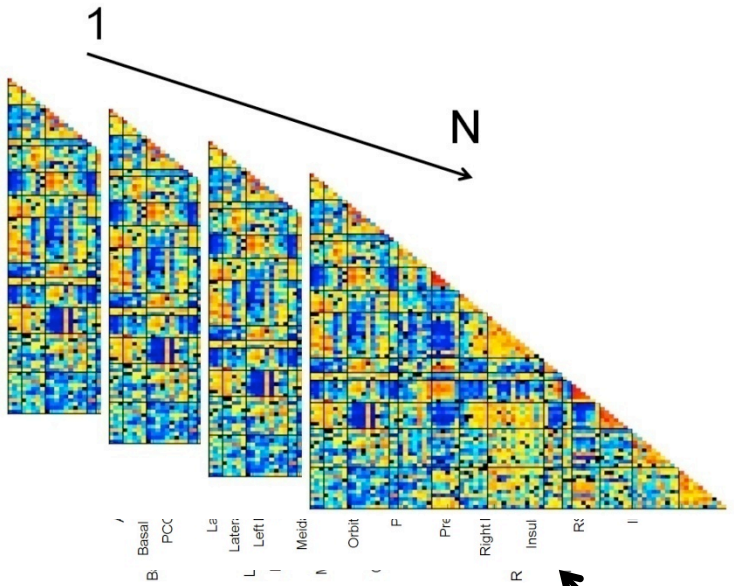
Machulda et al., *Arch Neurol*, 2011

Whole-Brain Connectivity in Alzheimer's Disease

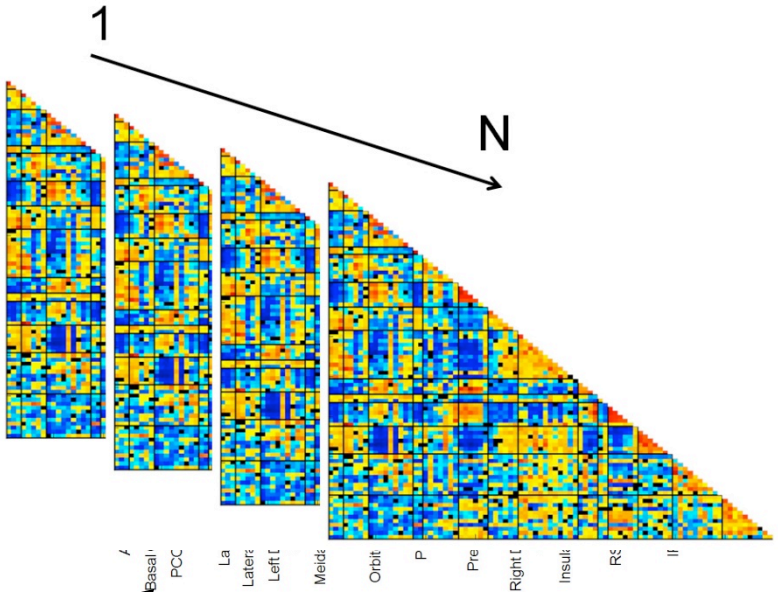


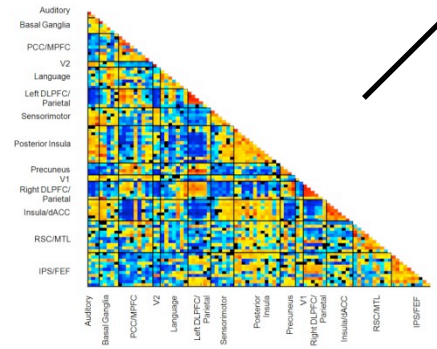
Classification

Controls



Patients



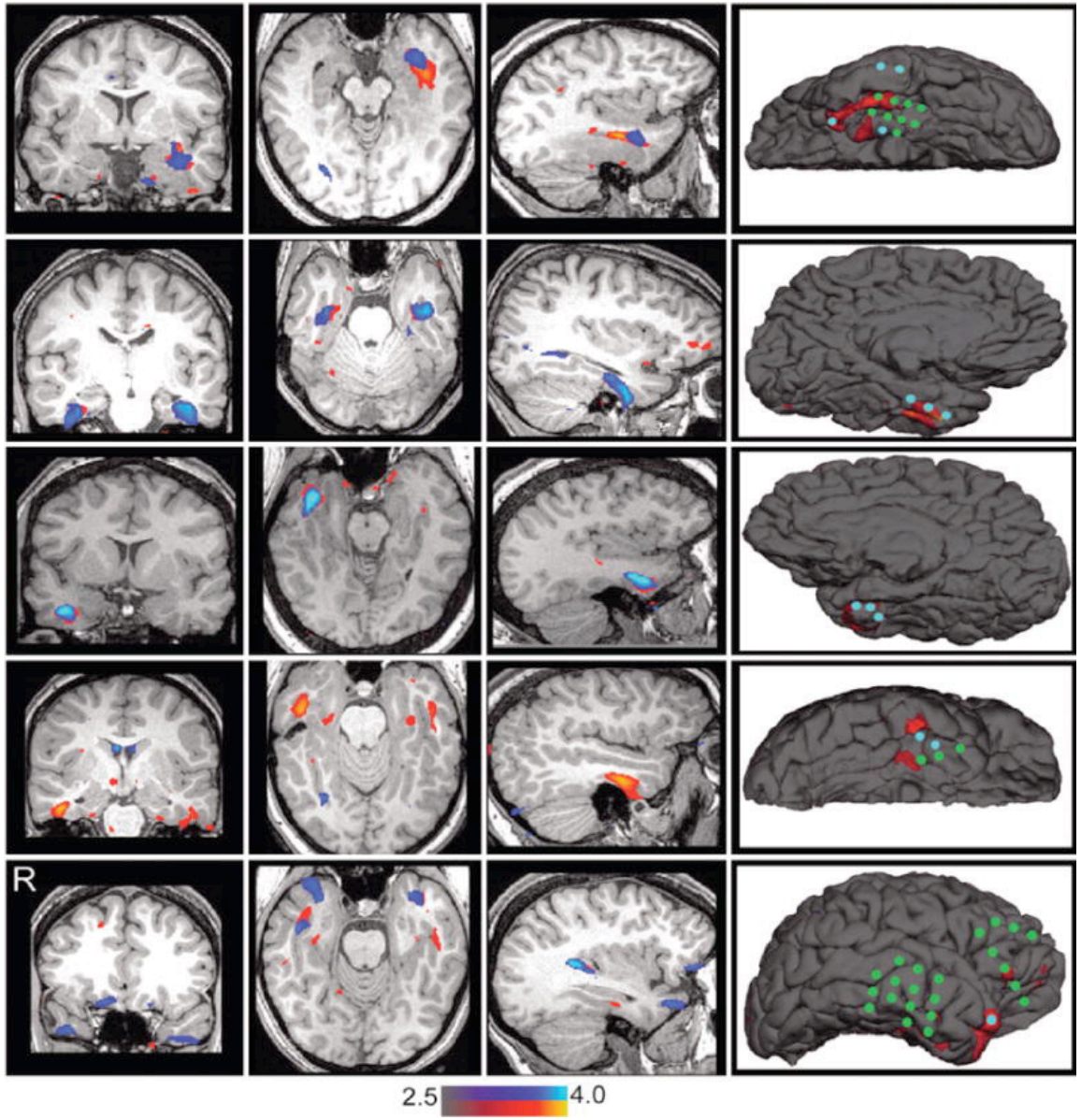


Fit = 0.97

Fit = 0.35

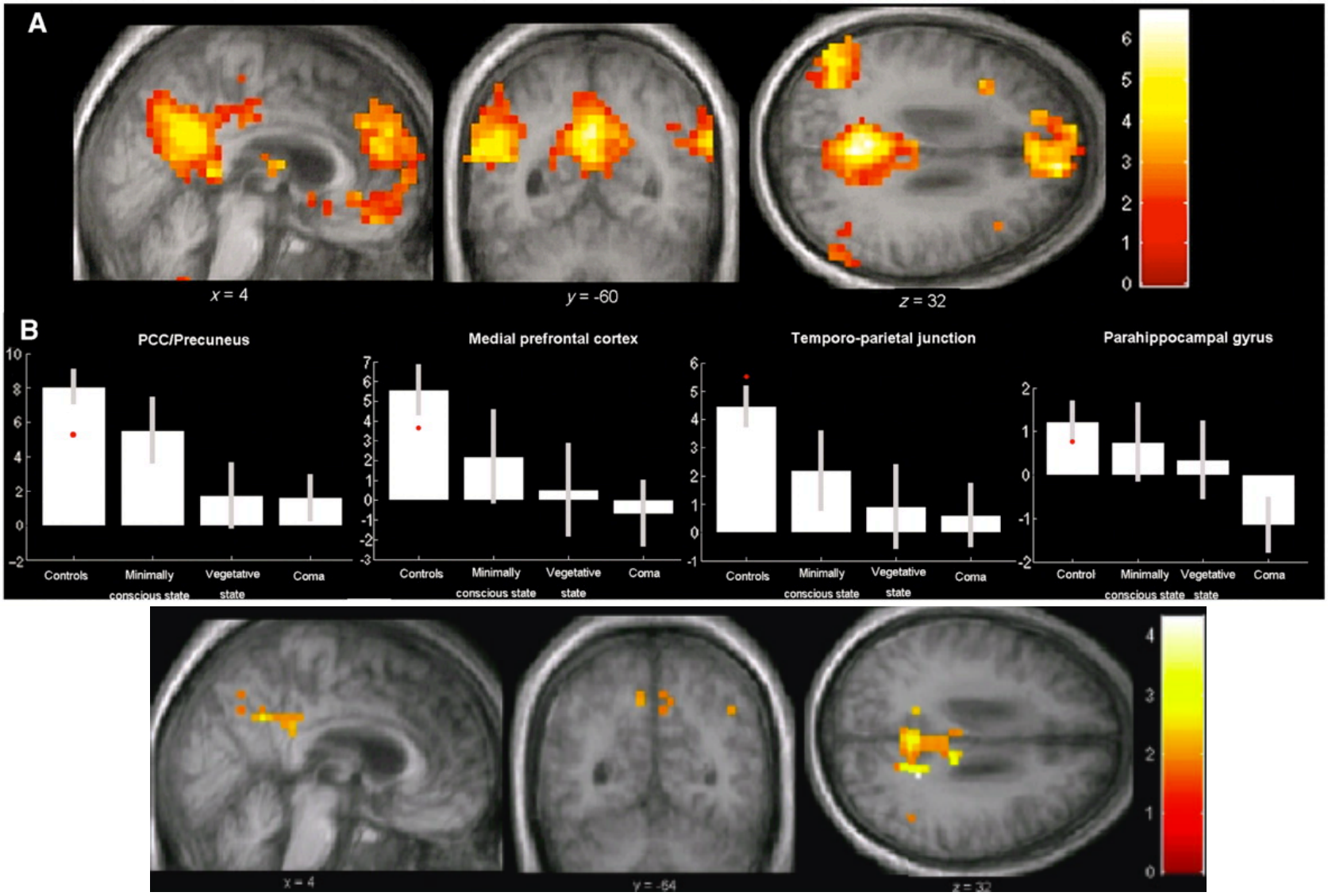
Single-Patient Level: Seizure Focus Localization

Increased
remote and local
connectivity



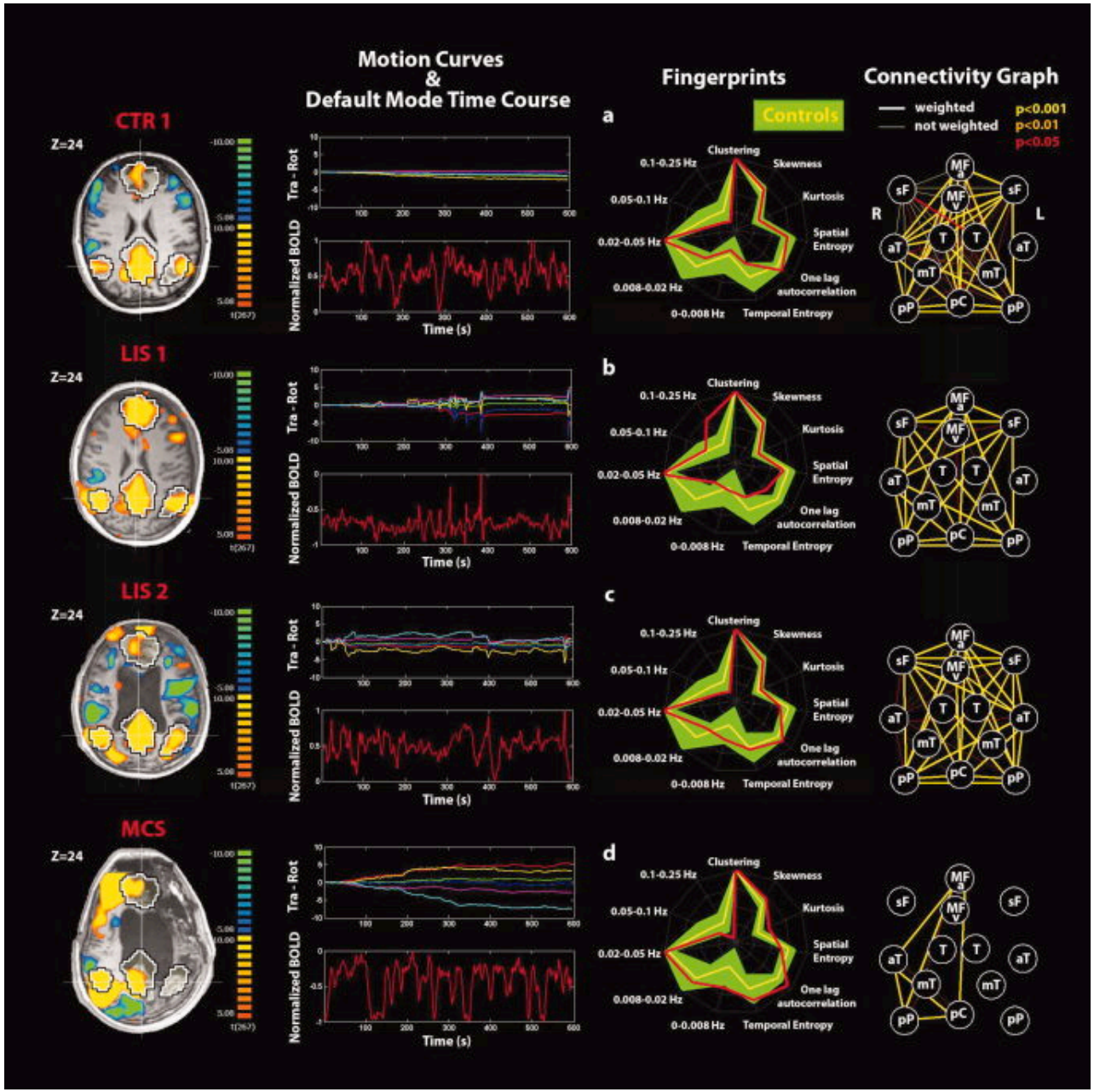
Stufflebeam et al., *J Neurosurg*, 2011

Prognosis for Coma Recovery



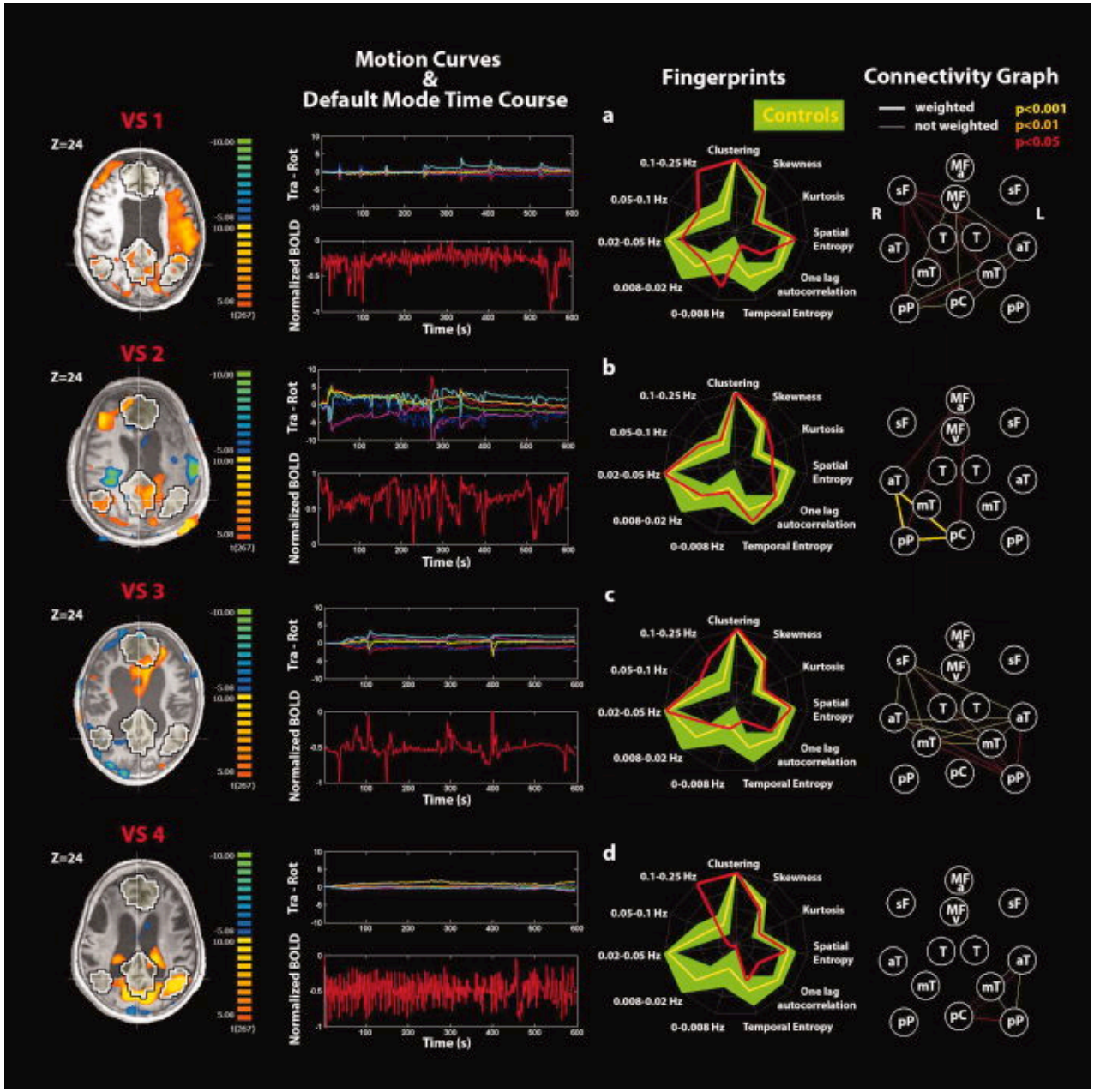
Vanhaudenhuyse et al., *Brain*, 2010

Single-Patient Level: Disorders of Consciousness



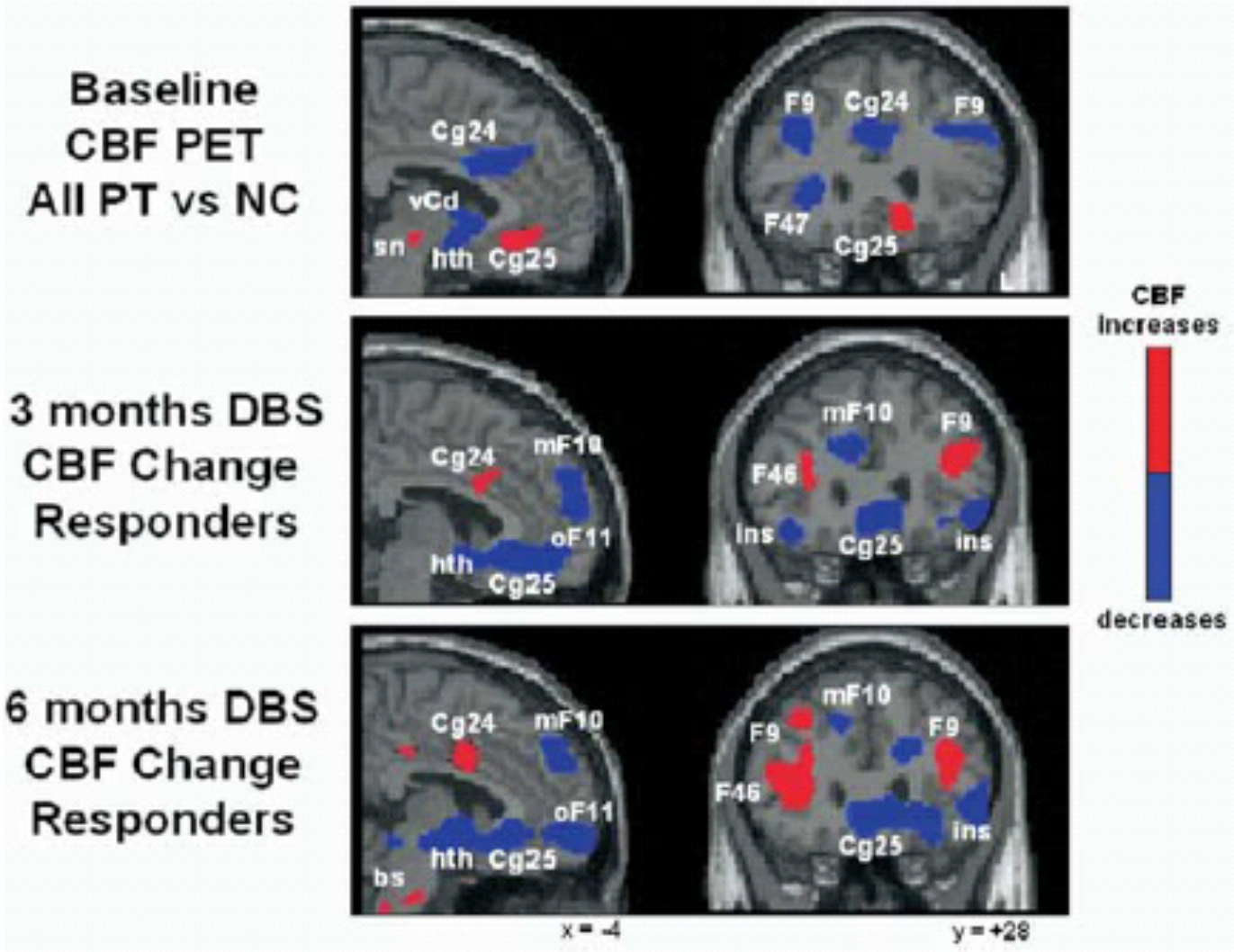
Soddu et al.,
Hum Brain Mapp, 2011

Single-Patient Level: Disorders of Consciousness



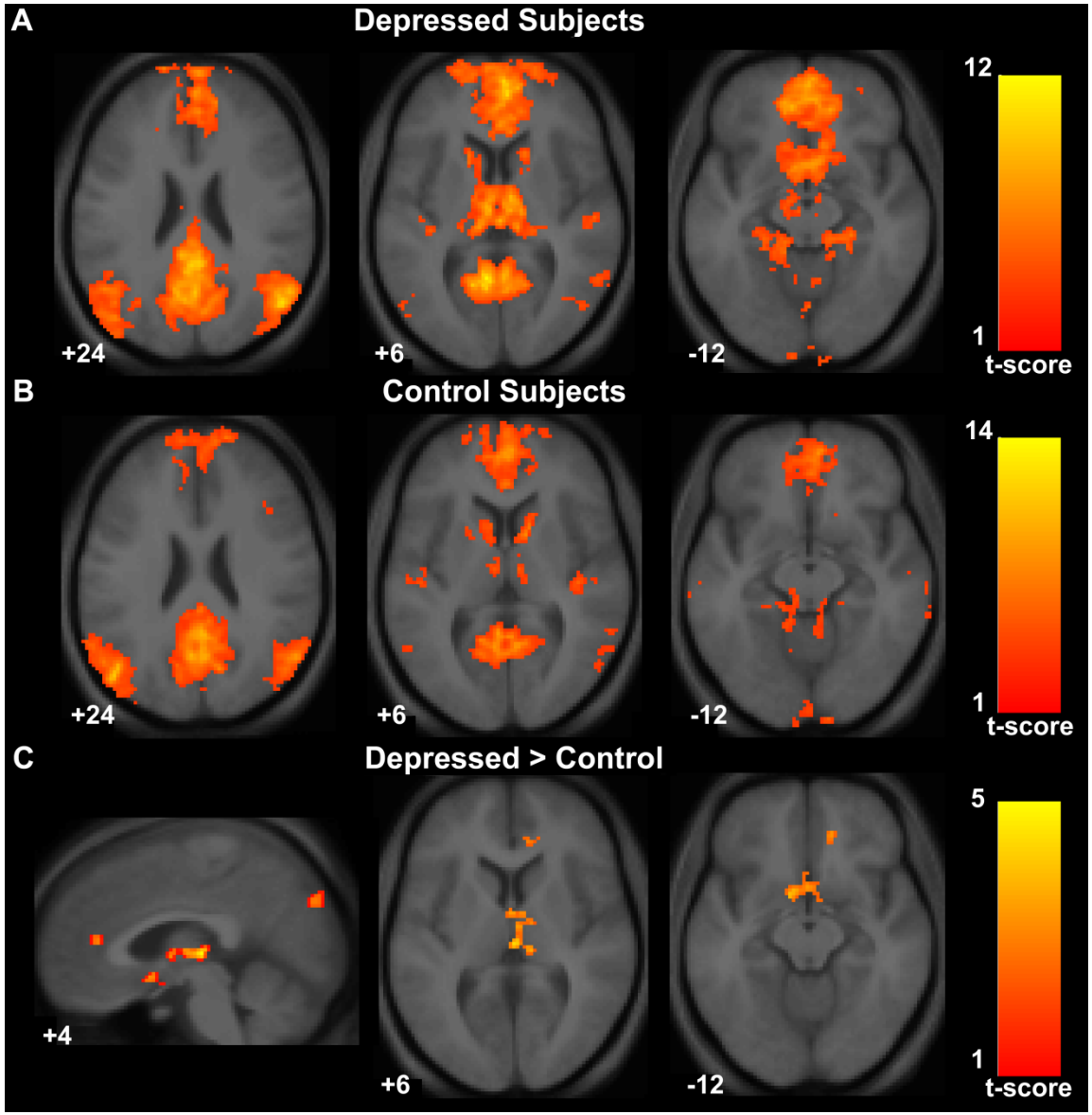
Soddu et al.,
Hum Brain Mapp, 2011

The Subgenual Cingulate in Depression



Mayberg et al., *Neuron*, 2005

Increased Subgenual Cingulate Connectivity in Depression

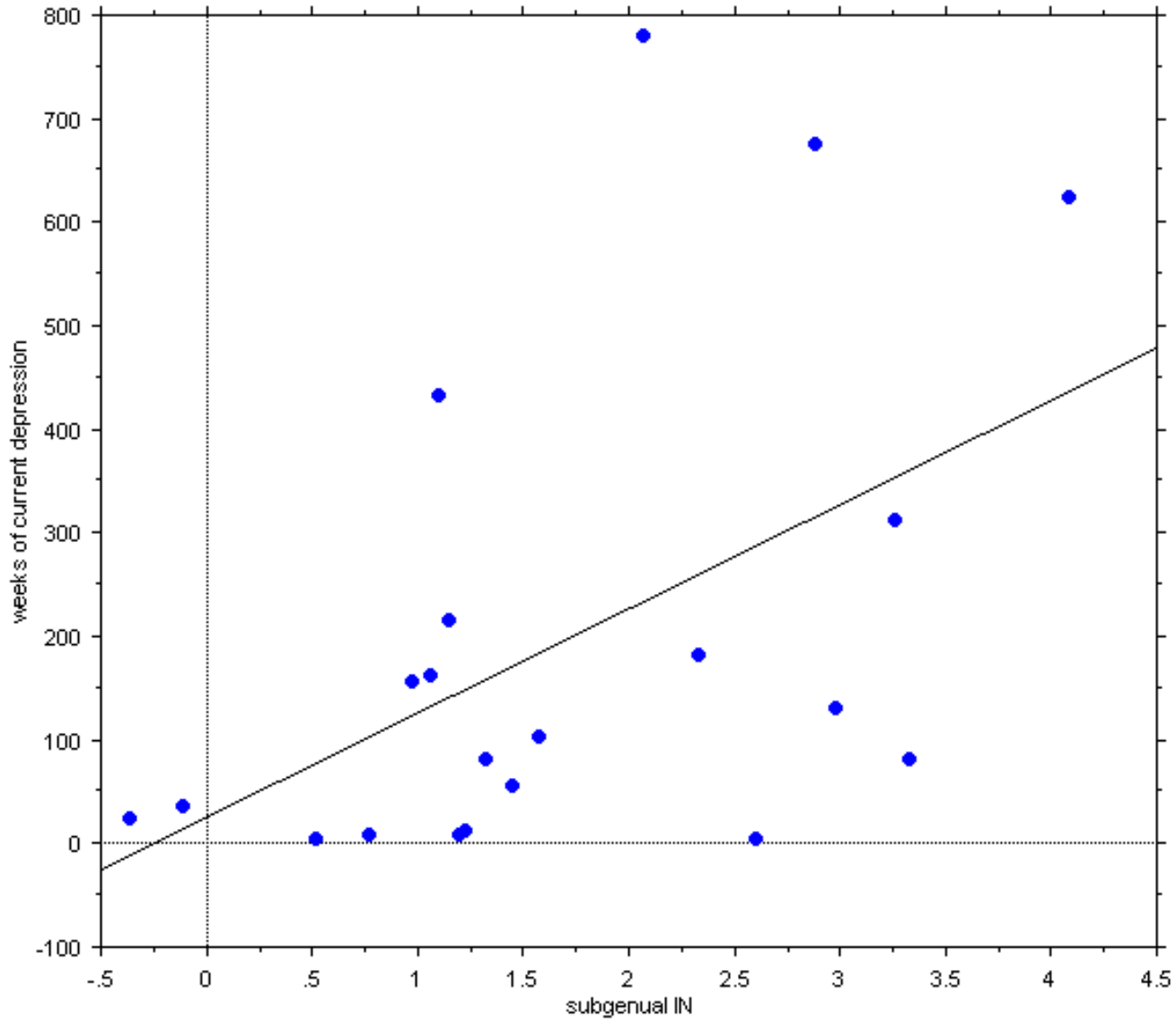


Greicius et al., *Biol Psychiatry*, 2007

BA25 Connectivity Correlates with Current Episode Duration

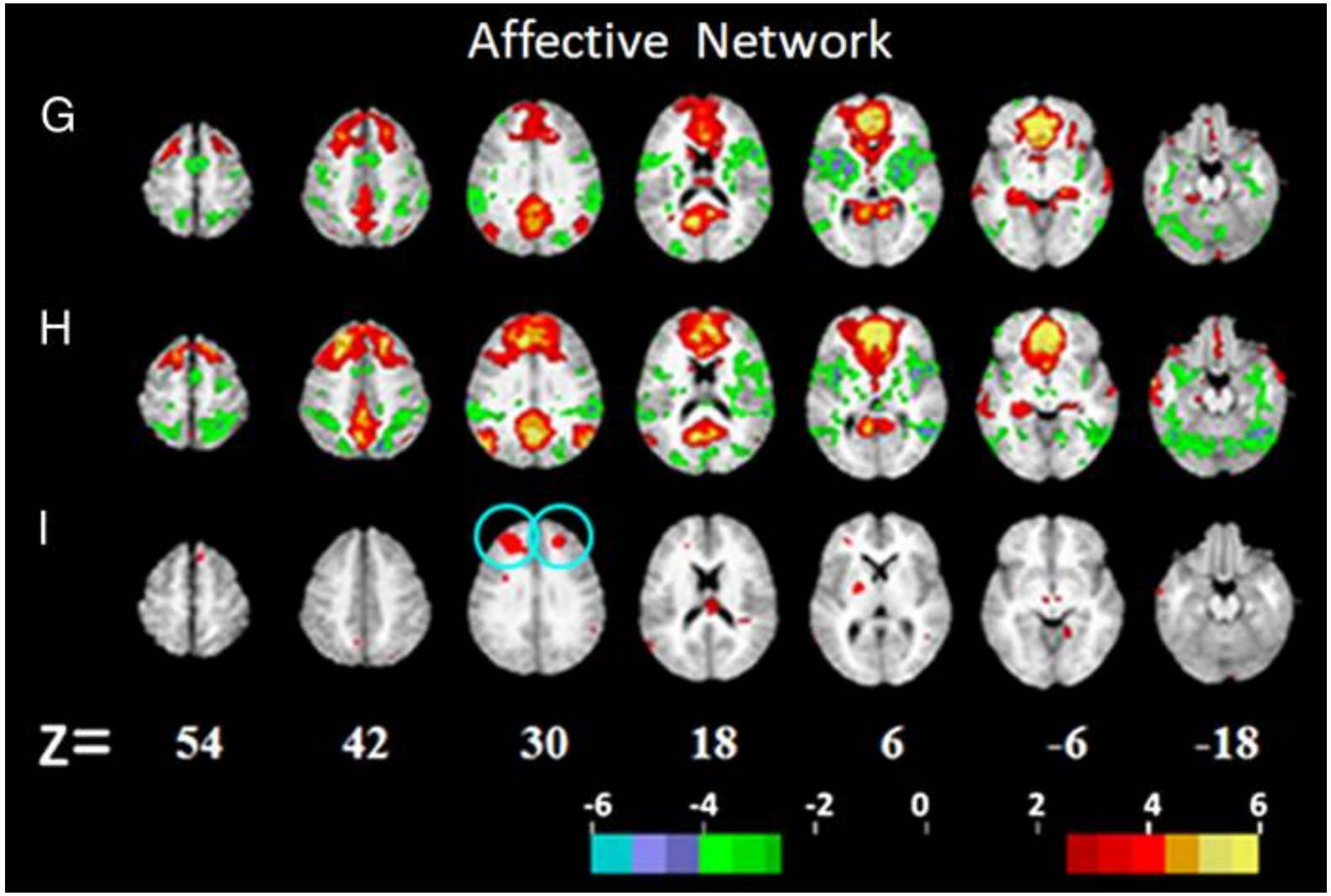
r = 0.49

p < 0.05



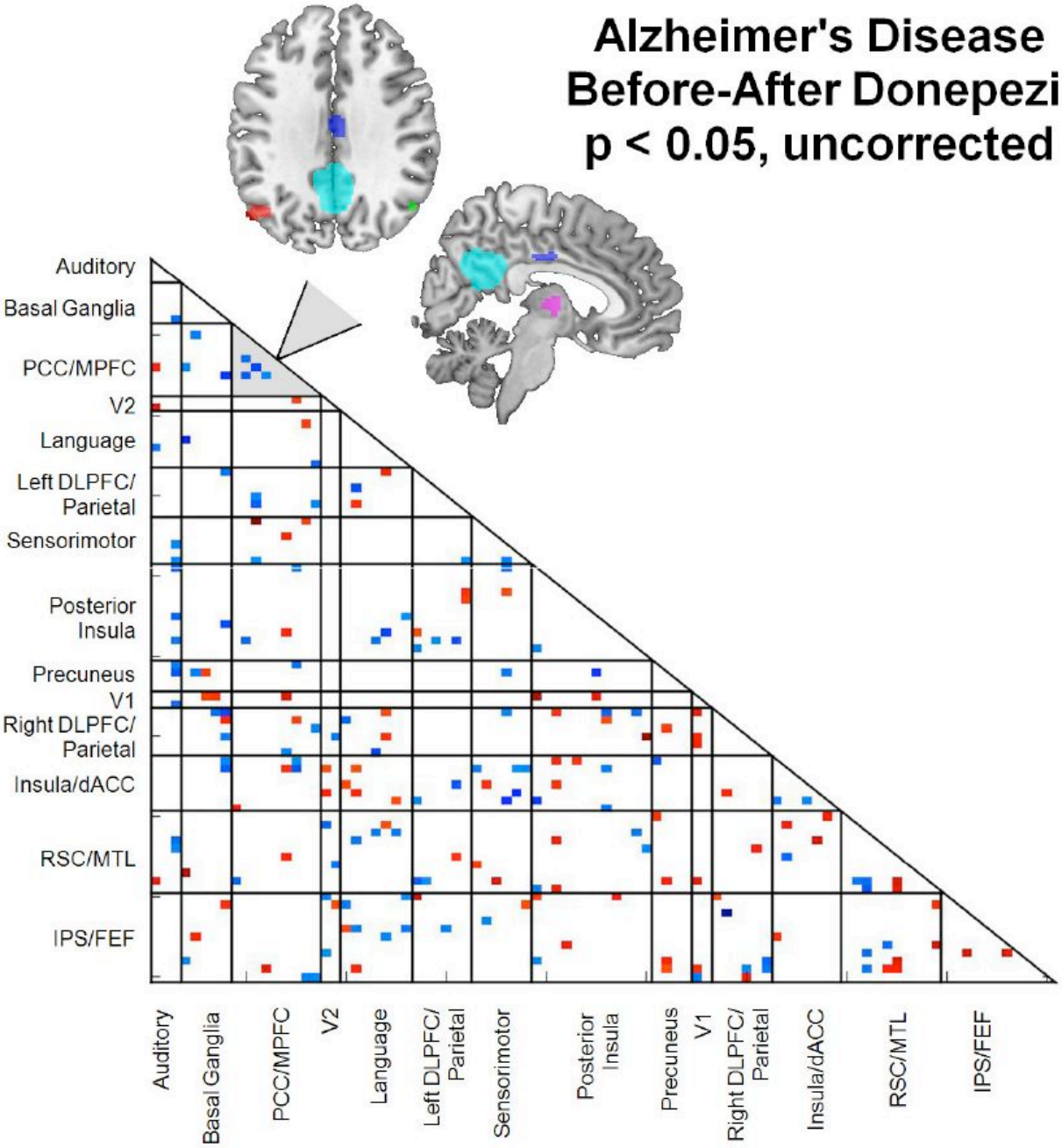
Greicius et al., *Biol Psychiatry*, 2007

Increased Subgenual Connectivity in Depression 2



Sheline et al., *PNAS* 2010

Alzheimer's Disease
Before-After Donepezil
# p < 0.05, uncorrected



Test-Retest Reliability

Table 7

Voxelwise analysis: Significant and Reliable Functional Connectivity

Seed ROI	BA	X	Y	Z	Z-Score	Multi-Scan		Inter-Session		Intra-Session	
						Mean	Max	Mean	Max	Mean	Max
PCC POSITIVE CONNECTIVITY											
L PCC	29/30	6	58	28	12.1	0.65	0.80	0.61	0.82	0.64	0.77
L vmPFC	10/11	6	-54	-4	7.7	0.54	0.64	0.37	0.58	0.65	0.81
L ITG	21	64	12	−18	7.6	0.69	0.84	0.55	0.82	0.61	0.75
R MFG	11	-4	-38	-18	7.6	0.50	0.68	0.49	0.75	0.43	0.69
L precuneus	19	38	80	36	7.4	0.54	0.67	0.36	0.57	0.41	0.64
L medial PFC	9	8	−48	34	7.3	0.07	0.66	0.22	0.60	0.01	0.69
R medial PFC	9/10	−12	−58	12	6.9	0.55	0.69	0.43	0.67	0.61	0.78
R ITG	21	−62	8	−22	6.8	0.57	0.65	0.50	0.68	0.57	0.74
R MFG	8	−24	−24	44	6.7	0.65	0.79	0.57	0.80	0.67	0.77
R MTG		−48	62	26	6.5	0.79	0.87	0.71	0.86	0.74	0.90
L lingual gyrus	18	10	56	4	6.5	0.48	0.69	0.61	0.77	0.26	0.62
L SFG	6	20	−28	38	6.5	0.64	0.78	0.51	0.77	0.64	0.79
PCC Negative Connectivity											
L anterior insula		38	2	−2	−7.3	0.33	0.60	0.25	0.62	0.29	0.56
R anterior insula		−40	−2	−4	−7.2	0.41	0.73	0.42	0.76	0.36	0.73
R precentral gyrus	6	−58	−10	2	−7.2	0.75	0.83	0.71	0.77	0.69	0.78
BL SMA/preSMA		−2	−6	48	−7.0	0.42	0.59	0.39	0.68	0.50	0.78
L IPL		62	30	22	−7.0	0.51	0.73	0.52	0.71	0.41	0.73
R SFG	6	−20	4	62	−7.0	0.07	0.48	0.13	0.40	0.01	0.56
R AG	39	−62	36	34	−6.6	0.57	0.72	0.52	0.75	0.52	0.64
L MOG	19	54	66	−10	−6.6	0.64	0.72	0.42	0.58	0.58	0.66
R IFG	45	−46	−42	6	−6.5	0.62	0.72	0.55	0.68	0.58	0.72
R precentral gyrus	6	−48	0	38	-6.5	0.50	0.68	0.39	0.68	0.45	0.64
L precentral gyrus	6	58	−2	8	−6.4	0.49	0.72	0.36	0.59	0.59	0.73
L MFG	46	38	−40	22	−6.4	0.49	0.65	0.40	0.64	0.53	0.75

Shehzad et al., Cereb Cortex, 2009

Conclusions

- Intrinsic connectivity network strength reflects cognitive and emotional attributes
- Evoked behavior and responses abide by the tyranny of spontaneous fluctuations
- Connectivity allows exploration of continuous, subject-driven states
- Numerous potential clinical applications for diagnostics and gauging response to treatment
  - Pharmaceutical companies adding resting state as a biomarker
  - ADNI 2 has resting-state data (already online)

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